RIGHT MEDIAN NERVE ELECTRICAL STIMULATION TO IMPROVE AROUSAL AND RESPONSIVENESS OF PATIENTS IN VEGETATIVE OR MINIMALLY CONSCIOUS STATE FOLLOWING ACQUIRED BRAIN INJURY- A RANDOMIZED CONTROLLED TRIAL

Dissertation submitted to the Tamil Nadu Dr. MGR Medical University, Chennai, in partial fulfilment of requirements for the MD Branch XIX (Physical Medicine and Rehabilitation) examination in March 2016

DECLARATION

I hereby declare that "Right Median nerve electrical stimulation to improve arousal and responsiveness of patients in vegetative or minimally conscious state following acquired brain injury- A Randomized controlled trial" is my bona fide work in partial fulfilment of the requirement of the Tamil Nadu Dr MGR Medical University, Chennai, for the MD Branch XIX (Physical Medicine and Rehabilitation) examination in March 2016.

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CERTIFICATE

This is to certify that “Right Median nerve electrical stimulation to improve arousal and responsiveness of patients in vegetative or minimally conscious state following acquired brain injury- A Randomized controlled trial” is the bona fide work of Dr. Remya Mathew, Candidate Number 201329054, in partial fulfilment of the requirement of the Tamil Nadu Dr MGR Medical University, Chennai, for the MD Branch XIX(Physical Medicine and Rehabilitation) examination in March 2016, done under my supervision and guidance.

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Dr. Alfred Job Daniel
Principal
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"The Lord is your keeper, the Lord is your shade at your right hand."
Psalms 121:5

I would like to express my deep gratitude to my guide Dr. Raji Thomas whose advice, support, patience , enthusiasm and experience in neurorehabilitation, to explore a new and less known field has helped me successfully complete this study. I would like to thank Dr. George Tharion, Professor and Head of the Department of PMR for his support and encouragement for this study .

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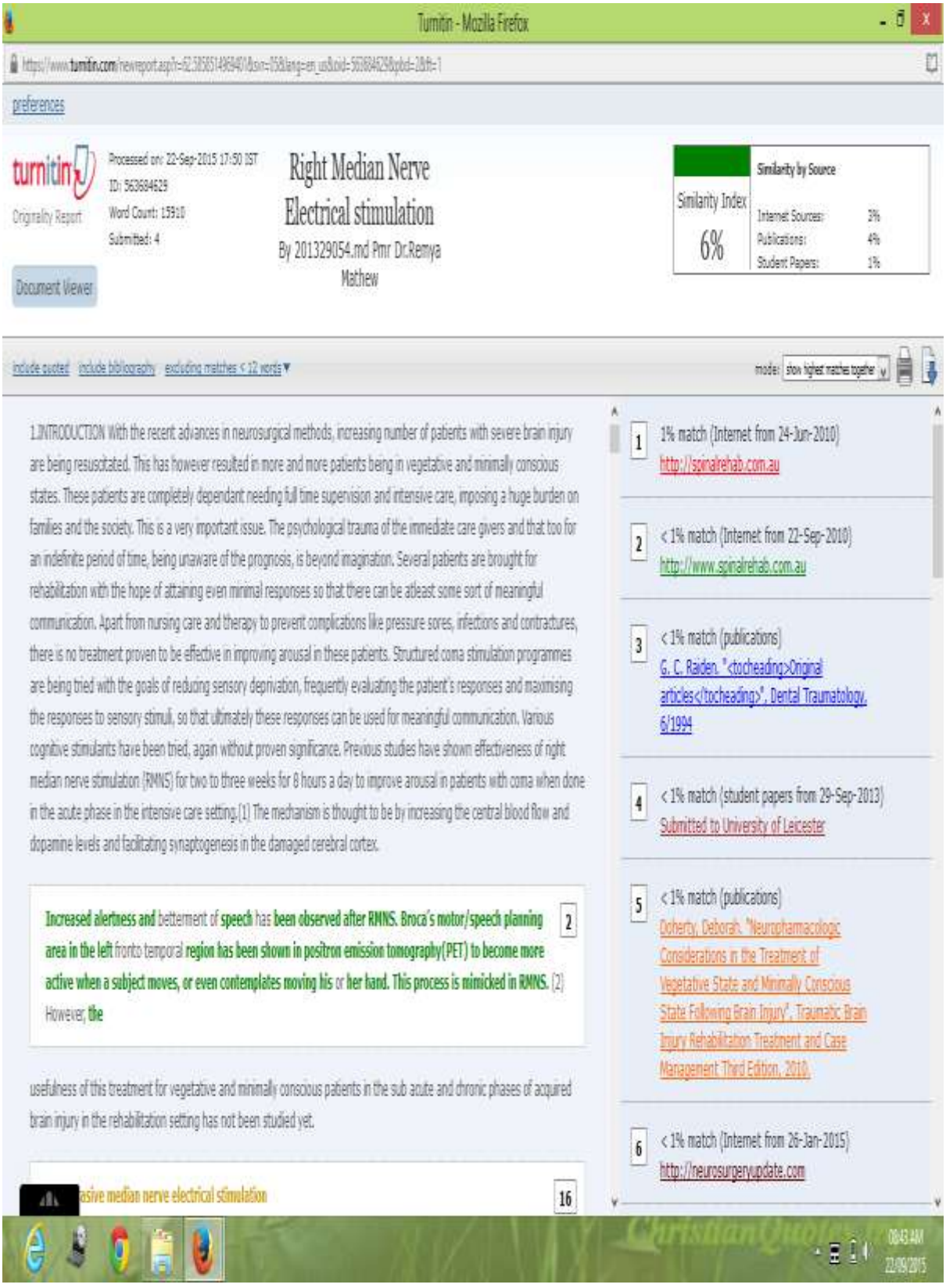
Remya Mathew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1.INTRODUCTION With the recent advances in neurosurgical methods, increasing number of patients with severe brain injury are being resuscitated. This has however resulted in more and more patients being in vegetative and minimally conscious states. These patients are completely dependant needing full time supervision and intensive care, imposing a huge burden on families and the society. This is a very important issue. The psychological trauma of the immediate care givers and that too for an indefinite period of time, being unaware of the prognosis, is beyond imagination. Several patients are brought for rehabilitation with the hope of attaining even minimal responses so that there can be atleast some sort of meaningful communication. Apart from nursing care and therapy to prevent complications like pressure sores, infections and contractures, there is no treatment proven to be effective in improving arousal in these patients. Structured coma stimulation programmes are being tried with the goals of reducing sensory deprivation, frequently evaluating the patient's responses and maximising the responses to sensory stimuli, so that ultimately these responses can be used for meaningful communication. Various cognitive stimulants have been tried, again without proven significance. Previous studies have shown effectiveness of right median nerve stimulation (RMNS) for two to three weeks for 8 hours a day to improve arousal in patients with coma when done in the acute phase in the intensive care setting.(1) The mechanism is thought to be by increasing the central blood flow and dopamine levels and facilitating synaptogenesis in the damaged cerebral cortex.
Increased alertness and betterment of speech has been observed after RMNS. Broca's motor/speech planning area in the left fronto temporal region has been shown in positron emission tomography(PET) to become more active when a subject moves, or even contemplates moving his or her hand. This process is mimicked in RMNS. (2) However, the
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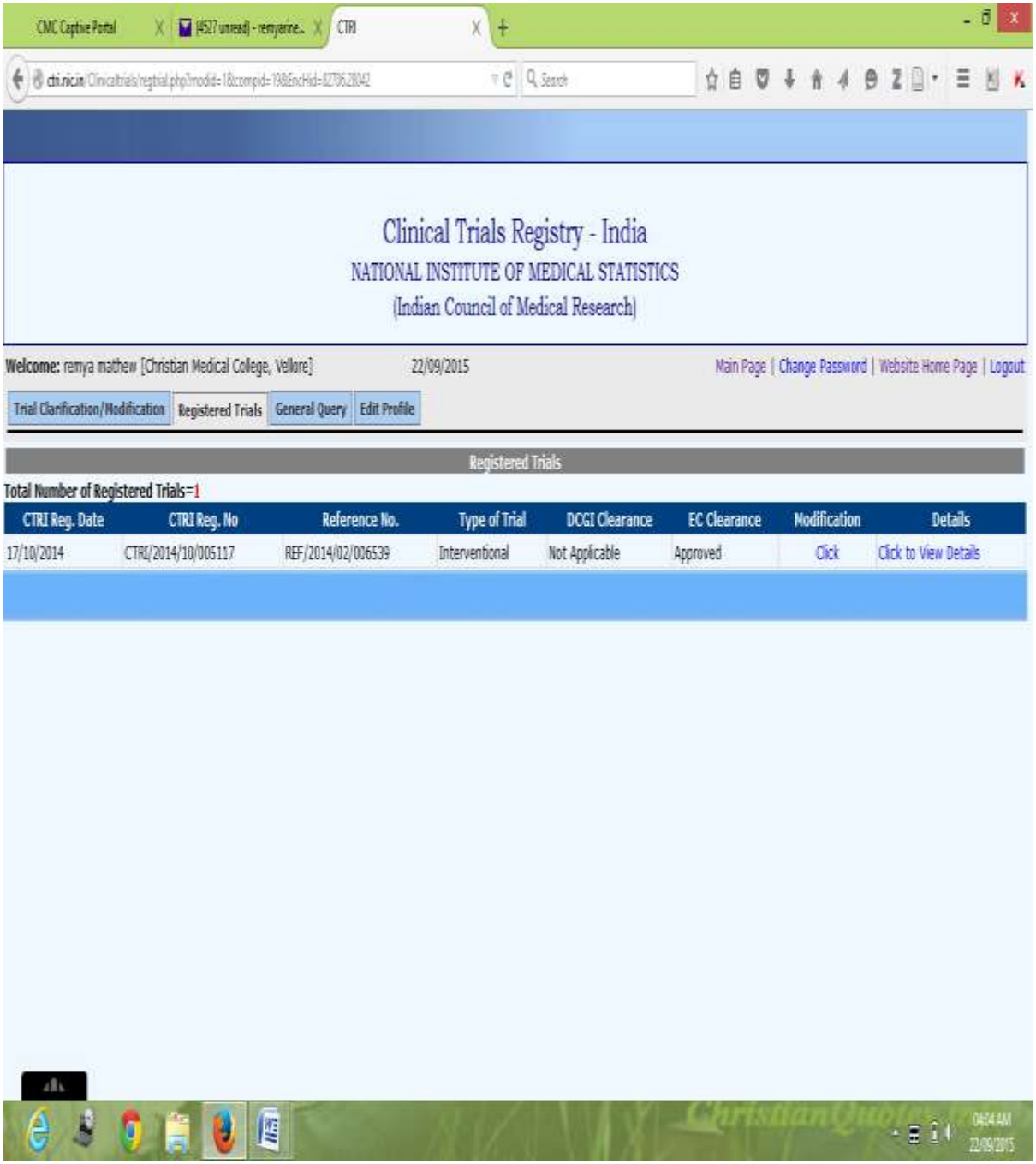
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LIST OF ABBREVIATIONS

ARAS- Ascending Reticular Activating System

BERA- Brainstem Evoked Auditory Response

CRSR- Coma Recovery Scale Revised

DAI- Diffuse Axonal Injury

DOC- Disorders Of Consciousness

FES- Functional Electrical Stimulation

GOSE- Glasgow Outcome Scale Extended

MCS- Minimally Conscious State

OT- Occupational Therapy

RLAS- Ranchos Los Amigos Scale

RMNS- Right Median Nerve Electrical Stimulation

SSEP- Somato Sensory Evoked Potential

TBI- Traumatic Brain Injury

VEP- Visual Evoked Potential

VS-Vegetative State

WHIM- Wessex Head Injury Matrix

TITLE OF THE STUDY

"Right Median nerve electrical stimulation to improve arousal and responsiveness of patients in vegetative or minimally conscious state following acquired brain injury- A Randomized controlled trial"

PLACE OF STUDY

Department of Physical Medicine and Rehabilitation
Christian Medical College, Vellore

ABSTRACT

AIM

To study the effectiveness of right median nerve electrical stimulation to improve arousal in patients in vegetative and minimally conscious states following acquired brain injury, of less than one and a half years duration.

OBJECTIVES

1. To test whether electrical stimulation of right median nerve produces statistically significant difference in the CRS, WHIM, GOSE and RLA scores.
2. To test whether electrical stimulation of right median nerve produces variation in the EEG pattern indicating arousal.

SUBJECTS AND METHODS

STUDY DESIGN-Randomized controlled double blind trial

PARTICIPANTS- Patients in vegetative and minimally conscious states following acquired brain injury were recruited from the inpatient wards of CMC hospital and Rehabilitation Institute. Total number of patients who completed the study was 24, with 11patients in the experimental group and 13patients in the control group. Statistical analysis was done for 24 patients.

INTERVENTIONS- In the experimental group, stimulation was done with Functional Electrical Stimulator (FES) with the standard operating protocol as Frequency= 40 Hz; Current=20mAmps; Pulse width=300μsec; on duration=20sec/min. Total 40 sessions of therapy, each session lasting for one hour was given. The control group received sham stimulation. Both groups received the standard coma stimulation programme.

OUTCOME MEASURES-The primary outcome measures were 1. CRS-R (Coma Recovery Scale Revised) 2. WHIM Score (Wessex Head Injury Matrix score), 3. RLAS (Ranchos Los Amigos Scale) and 4. GOSE

(Glasgow Outcome Scale Extended) . The secondary outcome measure was EEG.

RESULTS

The improvement in the level of consciousness as measured by CRSR, WHIM Total, WHIM Maximum, GOSE and RLA scores of patients in the intervention group was not significantly different from that observed in the control group.(p=0.57, p=0.36, p=0.68,p=0.97, p=0.80 respectively) Analysis of the CRSR subscales also did not show any statistically significant difference between the two groups.Subgroup analysis of patients with positive SSEP median showed statistically significant difference between the two groups in the improvement in CRSR score (p=0.02)The highest scores attained in the CRSR,WHIM Total and GOSE scores was seen in the intervention group. The maximum score attained in the Visual, Motor, Oromotor and Communication scales were higher in RMNS group in comparison with the control group. The change in the EEG Pattern was not different between the two groups.

In both the groups, patients with DAI had a better percentage increase in the median value of CRSR score(p=0.02)Patients with absence of abnormal posturing and positive BERA results had statistically significant association with the improvement in WHIM Maximum(p=0.01 and p=0.04) and WHIM Total scores.(p=0.04 and 0.008).Patients in minimally conscious state showed statistically significant improvement in the RLA(p=0.006) and GOSE scores. (p= 0.02).

Normal cortical wave pattern in SSEP median, VEP and BERA studies and presence of P14 wave obtained in SSEP median study are associated with better outcomes. None of the patients had any adverse effects during the procedure which was completely non-invasive.

More careful selection criteria for inclusion of patients and a larger sample size with more hours of stimulation over a longer duration may show significant results, so that right median nerve stimulation can be an useful adjunct in the management of patients in vegetative and minimally conscious states.

KEY WORDS:
Disorders of consciousness, Vegetative state, Minimally conscious state, Right Median nerve stimulation, CRSR, WHIM,RLAS and GOSE scales, SSEP Median, BERA, Diffuse axonal injury, Coma stimulation.

1.**INTRODUCTION**

With the recent advances in neurosurgical methods, increasing number of patients with severe brain injury are being resuscitated. This has however resulted in more and more patients being in vegetative and minimally conscious states. These patients are completely dependant needing full time supervision and intensive care, imposing a huge burden on families and the society. This is a very important issue. The psychological trauma of the immediate care givers and that too for an indefinite period of time, being unaware of the prognosis, is beyond imagination. Several patients are brought for rehabilitation with the hope of attaining even minimal responses so that there can be atleast some sort of meaningful communication.

Apart from nursing care and therapy to prevent complications like pressure sores, infections and contractures, there is no treatment proven to be effective in improving arousal in these patients. Structured coma stimulation programmes are being tried with the goals of reducing sensory deprivation, frequently evaluating the patient's responses and maximising the responses to sensory stimuli, so that ultimately these responses can be used for meaningful communication. Various cognitive stimulants have been tried, again without proven significance.

Previous studies have shown effectiveness of right median nerve stimulation (RMNS) for two to three weeks for 8 hours a day to improve arousal in patients with coma when done in the acute phase in the intensive care setting.(1) The mechanism is thought to be by increasing the central blood flow and dopamine levels and facilitating synaptogenesis in the damaged cerebral cortex. Increased alertness and betterment of speech has been observed after RMNS. Broca's motor/speech planning area in the left fronto temporal region has been shown in positron emission tomography(PET) to become more active when a subject

moves, or even contemplates moving his or her hand. This process is mimicked in RMNS. (2)

However, the usefulness of this treatment for vegetative and minimally conscious patients in the sub acute and chronic phases of acquired brain injury in the rehabilitation setting has not been studied yet. Non invasive median nerve electrical stimulation can be done with little risk and is cost effective. There have been no major complications induced by peripheral electrical stimulation.(3)

This study aims to evaluate the effectiveness of right median nerve electrical stimulation to improve arousal in patients with disorders of consciousness in the rehabilitation setting. Patients with duration of injury upto one and a half years will be included in the study. The intervention arm will receive median nerve stimulation while the control arm will receive sham stimulation. Both groups will undergo the standard coma stimulation programme. The outcome will be assessed using the Coma Recovery Scale, Wessex Head Injury Matrix Score, Glasgow Outcome Score Expanded and The Ranchos Los Amigos Scale. EEG will be used as a secondary outcome measure. If proven to be effective, RMNS could be an additional treatment modality for this group of patients.

2. JUSTIFICATION

Patients with disorders of consciousness including vegetative and minimally conscious states present a continuous struggle for their families and pose a major medical and social challenge. There are no standard protocols of treatment available for improving consciousness in these patients. Various medications have been tried to improve arousal with no proven benefits.

In the last decade, right median nerve stimulation has been tried for improving arousal from of acute coma after traumatic brain injury. However, the use of this technique for patients in vegetative and minimally conscious states in the subacute and chronic phases of acquired brain injury to improve arousal is relatively new. The technique is noninvasive and safe without any risk of complications.

Minimal improvement of responses is also worthwhile because as the wakefulness and arousal increases they can be more responsive to the standard modalities of coma stimulation like visual/auditory stimulations, swallow training etc. Moreover communication can be trained as the internal awareness increases. It may eventually give a better patient care satisfaction for the family and lead on to better responses.

3.AIM AND OBJECTIVES

AIM:

To study the effectiveness of right median nerve electrical stimulation in improving arousal in patients in vegetative and minimally conscious states following acquired brain injury, of less than one and a half years duration.

OBJECTIVES:

1.To test whether electrical stimulation of right median nerve produces statistically significant differences in the CRS, WHIM, GOSE and RLA scores in patients in vegetative or minimally conscious states secondary to severe acquired brain injury of less than one and a half years duration.

2. To test whether electrical stimulation of right median nerve produces variation in the EEG pattern indicating arousal in patients in vegetative or minimally conscious states secondary to severe acquired brain injury of less than one and a half years duration.

4. REVIEW OF LITERATURE

4.1. COMMON CAUSES OF ACQUIRED BRAIN INJURIES.

Trauma due to direct impact, cerebrovascular accidents, hypoxia or hypo-perfusion due to cardio respiratory arrest ,profound blood volume loss, infection, inflammation, encephalitis, vasculitis due to autoimmune causes, toxic or metabolic causes like drug or alcohol poisoning and severe hypoglycaemia, tumours, progressive neurodegenerative conditions like Alzheimer's disease etc are the common causes resulting in acquired brain injury.(4)

4.2 TRAUMATIC BRAIN INJURY

The main cause of acquired brain injury is trauma. Morbidity and mortality rate after traumatic brain injury is quite high. Disability burden after the brain injury, is increasing in an alarming rate in India compared to other developing countries. In India, roughly 1.5 to 2 million persons sustain brain injury every year with a death rate of 1 million per year. The major cause of traumatic brain injuries (TBI) is road traffic accidents(60%), which is followed by falls (20%-25%) and violence and assaults (10%). 15%-20% of TBI are due to illegal driving after alcohol consumption.

The demand for rehabilitation of brain injured patients is progressively on the rise. This is a major challenge now faced by India and other developing countries.(5)

4.3. PATHOLOGY OF TRAUMATIC BRAIN INJURY

The pathophysiology of TBI includes a primary injury and secondary injury. In primary injury, brain tissue is damaged during the injury. In secondary injury

brain tissue is injured by various biochemical cascades, and by chronic degeneration and regeneration sequalae.

Primary injury:

The differential movement of the brain relative to the skull results in contusions. This happens often on the inferior surface of the frontal and anterior temporal lobes. They can occur beneath the impact site (coup injury) or opposite of the impact (contrecoup injuries).

Angular acceleration can lead to diffuse axonal injury (DAI). Severity and grade of DAI depends on the duration, magnitude and direction of the acceleration. Brain areas mainly affected by DAI are midline structures. DAI can result in impaired consciousness.

Laceration of dural veins and meningeal arteries can lead to epidural hematomas (EDH). This can result in sudden neurologic deterioration. Subdural hematomas (SDH) occur because of the tearing of bridging veins. Shearing of vessels in the subarachnoid space results in subarachnoid hemorrhage (SAH).

Secondary Injury

The initial impact can later result in secondary injuries. These occur because of the massive release of neurochemicals, edema in the brain parenchyma, and effect on ionic equilibrium in the brain.

Brain edema results in elevated intracranial pressure (ICP). Raised ICP in turn leads to herniation. While axons are stretched excitatory amino acids are released. This can lead to the influx of sodium and chloride ions, resulting in swelling of the neuronal cells. This is followed by the release of chemicals which damage the neuronal tissue, like nitric oxide, superoxide, and free radicals. These in turn damage the cellular DNA and cellular membranes, resulting in cell death.

Chronic degeneration, repair, and regeneration process sets in later as a result of various neuroprotective and neuro repair mechanisms.

4.4. SEVERITY OF BRAIN INJURY

Glasgow Coma Scale (GCS) is the initial assessment tool for determining the severityof traumatic brain injuries. This is based on visual, verbal and motor responses. This has scoring ranging from 3 to 15. Based on the GCS score, severity can be categorised into mild, moderate and severe brain injury. Severity of injury is also defined by the duration of loss of consciousness. (6)

4.5. CONSCIOUSNESS-DEFINITION AND CHARACTERISTICS

"Consciousness" is the function of the human mind that accepts and processes data, crystallizes it and then saves it or rejects it with the help of the five senses, mind's reasoning ability, emotions and imagination and memory." (7)

If consciousness is a coin, then wakefulness and awareness are its two sides.

1. When an individual is 'awake' often his eyes are open and there will be arousal of the motor system where as in sleep there is eye closure and motor quiescence. It can be assessed from the pattern of behavioural response. Assessment of wakefulness is possible with electrophysiological modalities like EEG also. Here we are able to elicit the waves of wakefulness or arousal. (6)

2. Ability to experience any sort of external stimuli is awareness. If the individual is able to appreciate and perceive self and surroundings and interact with others we assume there is awareness.(6)

4.6. DISORDERS OF CONSCIOUSNESS

Coma: It is a state of nonarousable unresponsiveness, lasting more than 6 hours. Here the person show absent awareness, loss of sleep wake rhythm and cannot

be awakened. He fails to respond normally to noxious, auditory or visual stimuli. (8)

Vegetative state (VS): It is a state of wakefulness without awareness. Here there will not be any arousal either spontaneous or induced by stimuli, but the individual will be wakeful. There is preserved sleep–wake rhythm and complete absence of a behavioural evidence for internal or environmental awareness.(8)

Minimally conscious state (MCS): This is a condition in which the individual has a minimal but consistent proof of behavioural response for internal and external stimuli. There will be presence of self- or environmental awareness. There will be focussing and tracking noted. Here the person shows wakefulness with minimal awareness.(8)

4.7. DIAGNOSIS OF VEGETATIVE AND MINIMALLY CONSCIOUS STATE

4.7.1. Diagnosis of Vegetative state(9)

Diagnosis of vegetative state is mainly by exclusion. Careful assessment is needed using validated tests. The two essential criteria required to diagnose vegetative state are

1. Absence of awareness and communication
2. Absence of sustained purposeful or voluntary behaviours.

4.7.2. Diagnosis of Minimally conscious state(9)

Here the individual follows simple commands. There are consistent gestures or verbal responses for the external stimuli. There can be intelligible vocalisation. Individual should be showing purposeful or relevant response to environmental stimuli.

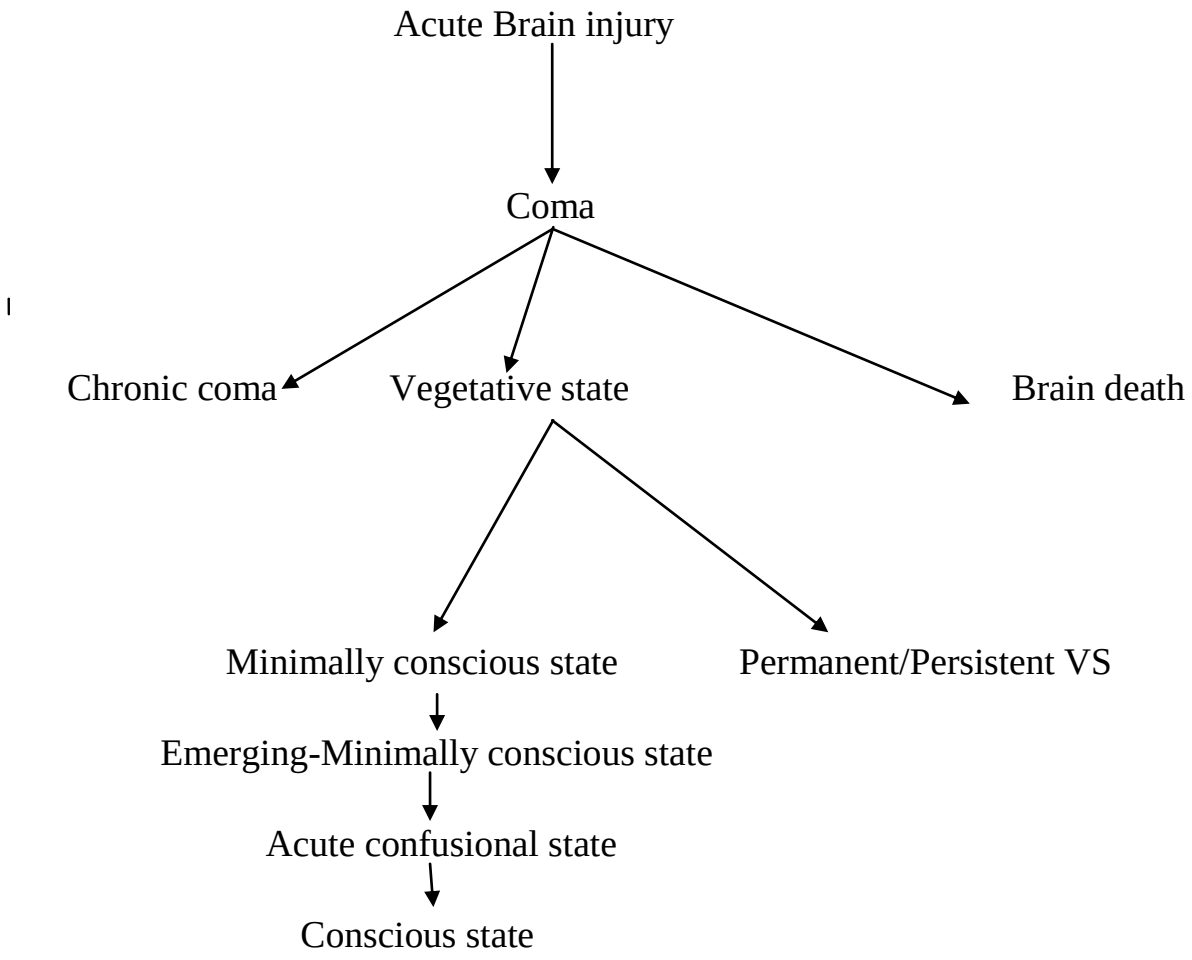


Figure: 4.1 Outcomes after severe traumatic brain injury

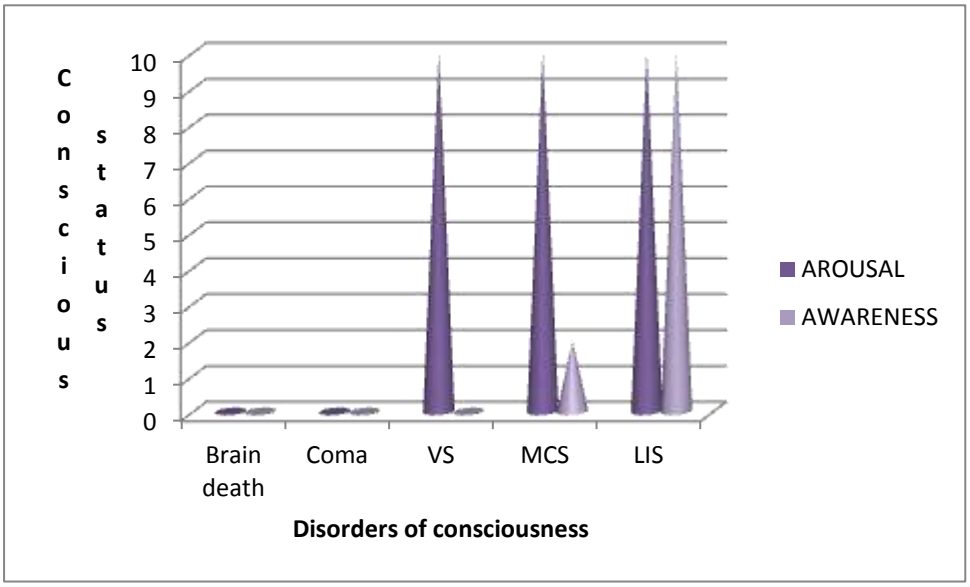


Figure 4.2: Level of arousal/awareness in various disorders of consciousness.

VS- Vegetative state

MCS- Minimally conscious state

LIS- Locked in syndrome

Behaviour	**COMA**	**VS**	**MCS**
Spontaneous eye opening	Absent	Present	Present
Motor response	Absent	Reflex movements	Automatic/ Object manipulation
Verbalization	Absent	Random Vocalisation	Intelligible words
Affective response	Absent	Random	Consistent
Visual response	Absent	Startle	Focussing/Tracking
Obeying commands	Absent	Absent	Inconsistent
Communication	Absent	Absent	Nonreliable

Table 4.1: *Behavioural features of various disorders of consciousness*

4.8. OTHER TERMINOLOGIES RELATED TO DISORDERS OF CONSCIOUSNESS

a. Emergence from minimally conscious state(EMC)

Behavioural responses to environmental stimuli can be inconsistent in MCS where as there will be reliable and consistent responses to external stimuli when the patient emerges from MCS. To diagnose this, there should be

i. interactive communication

ii. functional use of objects (i.e., demonstration of the use of 2 different familiar objects) (e.g., cup, comb) (6)

b. 'Permanent' MCS

A patient continuing in the state of MCS for 5 years post brain insult, with no demonstrable features towards improving responsiveness on serial testing is said to be in permanent MCS. Probability to recover is quite less in this type of disorder.

If there is history of severe anoxia, the label of 'Permanent' MCS can be given even after 3 to 4 years post brain injury.(10)

c.Prolonged disorders of consciousness

A patient showing wakefulness with reduction or absence in the response status for a period of about four weeks is said to be in a state of prolonged disorder of consciousness.(6)

d. 'Continuing' VS and MCS

For a patient to be called in 'continuing VS' he should be showing complete absence of responses to environmental stimuli for a period of about four weeks.

For a patient to be called in 'Continuing MCS' he or she should show inconsistent reproducible interaction with the external environment, for more than four weeks. (6)

e. 'Permanent' DOC

When the probability of the recovery of consciousness is almost nil, the state is termed as 'Permanent' DOC.(6)

4.9.DIFFERENTIAL DIAGNOSIS FOR DISORDERS OF CONSCIOUSNESS(6),(11)

'Locked-in syndrome' and 'brainstem death' are entirely different from DOC, but the presentation can be alike.

a. **Locked-in syndrome:**

   Jean-Dominique Bauby, a journalist by profession, has narrated about this neurological condition in his book, "The Diving Bell and the Butterfly:" This syndrome occurs due to the pathology in the brain stem. There will be preservation of consciousness i.e. the awareness and wakefulness will be preserved. Basilar artery thrombosis resulting in ventral pontine infarct is the most common cause.(60%) Patients have tetraplegia and anarthria. Cognitive state will be in the near normal range. Spontaneous eye opening is present. This state can mimic DOC especially, the vegetative state.

b. **Brainstem death:**

   In brain stem death, all functions of midbrain, pons and medulla will be absent. The life is preserved on mechanical ventilation for a short while, usually to enable the relatives to make decisions on issues like organ donation. Physiological function will not be maintained once the artificial supports are withdrawn. (6)

4.10. ASSESSMENT OF PATIENTS WITH DISORDERS OF CONSCIOUSNESS

For assessment patient should be medically stable. It should be done by a trained person using various scales of consciousness.

4.10.1.Scales of assessment(12)

As consciousness cannot be directly observed and measured, the behavioural patterns are assessed, based on which state of consciousness is made out.

Detection of behavioural signs of consciousness is vulnerable to interrater variability. It can be affected by unpredictable variations in arousal, underlying sensory motor issues, cognitive and language deficits which are unrecognised, influence of sedation and underlying sepsis or infections if any.(12)

Neurobehavioral Rating Scales include JFK Coma Recovery Scale – Revised (CRS-R), **Ranchos Los Amigos Scale (**RLAS), Wessex Head Injury Matrix (WHIM), Glasgow Outcome Scale Extended(GOSE), Glasgow Coma Scale(GCS), Full Outline of Un Responsiveness (FOUR), Sensory Modality Assessment and Rehabilitation Technique(SMART) etc.

a. JFK Coma Recovery Scale – Revised (CRS-R)(13)

The JFK Coma Recovery Scale – Revised (CRS-R) has a maximum score of 23 with six sub scales -auditory, arousal, communication, motor, oromotor and visual scales.

On the basis of behavioural responses to environmental stimuli, scoring will be done. There is a hierarchical representation for the responses from reflex responses to responses given with sound cognition. With the revised coma recovery scale, differentiation of VS and MCS is possible.

b. The Wessex Head Injury Matrix(WHIM)

Shiel et al. (2000) has put forward a scoring system to assess recovery in patients with DOC. It has 62 different hierarchically arranged points for the assessment of recovery from coma. There is good interrater agreement for this scoring system. This scale also exhibits very good test-retest reliability. (14)

c.Ranchos Los Amigos Scale (RLAS)

This scale assesses how much the patient is aware and cognitively sound enough to respond to stimuli from external environment. Scores range from 1 to 8. Each of the eight levels represent the typical sequential progression of recovery from brain damage. Score 1 indicates absent response and score 8 represents appropriate and purposeful functioning. Level 1 almost corresponds to coma state, Level 2 corresponds to vegetative state showing some reflexes without awareness and Level 3 corresponds to minimally conscious state with some amount of awareness. (15)

d.Glasgow Coma Scale (GCS)/ Glasgow Outcome Scale Extended(GOSE)

(16)**,**(17)

GCS is commonly used in acute settings like casualty or emergency departments for the initial recording of level of consciousness. DOC like VS or MCS cannot be diagnosed and graded with this scale validly.(18) According to GOSE scale, level 2 is Vegetative state (VS) and Level 3 (Lower severe disability) indicates that the patient needs full assistance in ADL throughout the day, which almost corresponds to minimally conscious state.(17)

e.The Sensory Modality Assessment and Rehabilitation Technique(SMART) (19)

Gill-Thwaites (in 1997) introduced a new scoring measure for disorder of consciousness named 'SMART'. Eight characters are assessed in five different strata. The eight features are auditory response, arousal, communication, olfactory and gustatory sensation, motor functions, tactile and visual responses. Gill-Thwaites and Mundey suggested that SMART can be a reliable tool to differentiate the awareness status in VS and MCS.

f.Full Outline of Unresponsiveness (FOUR)

Wijdicks et al. put forward an assessment tool for DOC patients named FOUR (Full Outline of Unresponsiveness) score. This scoring system has four features to be assessed -the respiratory function, brain stem function, motor response and visual response. Each character has a maximal score of four. This scoring system is better compared to the GCS as it provides the neurological status of the patient in a much more detailed manner. (20)

4.10.2. IMAGING

Brain imaging plays a major role in confirming the diagnosis and assessing the prognosis of disorders of consciousness states.

Neuroimaging and Outcome Assessment in DOC (21)

The two findings seen commonly e in the brain images of patients with disordered consciousness are necrosis of brain tissue especially in areas of cerebral cortex, brain stem and thalamic areas and Diffuse axonal injury, mainly due to shear effect sustained by axons of the neuronal cells.

a. Magnetic Resonance Imaging(21)

In traumatic coma, areas most commonly involved are the pons, midbrain, and basal ganglia .The bilateral involvement points to poor outcome. Shape analysis with MRI shows low thalamic volume in case of severe disorders of consciousness.

b.Functional Magnetic Resonance Imaging(f-MRI)

f-MRI is used to study the neuronal network associated with a defined task and behavioural responses. f-MRI has been used to assess and rate the interaction and communication ability of patients with disorders of consciousness by giving two different mental imagery tasks. Five out of 54 patients in the study showed response and the brain activity during the response was detected and recorded by f-MRI. (22)

c.Positron Emission Tomography(21)

PET can be used to assess the consciousness status. VS and MCS patients can be differentiated by the variation in the activation signals of medial parietal cortex and adjacent posterior cingulate cortex.

d.FDG-PET (Fluorodeoxyglucose - Positron Emission Tomography)

Neural networks for internal and external awareness influence the consciousness status of an individual. It encompasses the frontoparietal associative cortices, cingulate gyrus, precuneus, and thalamus areas of the brain. (FDG) PET can detect the neural activity in these areas. This test assess the glucose metabolism rate at various regions of the brain. In VS and MCS patients reduction in the metabolic function in the frontoparietal associative cortices can be seen. (22)

e.Diffusion Tensor Imaging (DTI)

Thalamic and sub cortical white matter structural integrity is strongly related to the diagnosis of disorders of consciousness. 95% accuracy exists in the differential diagnosis of VS and MCS states with DTI.(21)

f.Magnetic Resonance Spectroscopy(21)

It mainly works with the quantification of 4 neurochemical metabolites: creatine-phosphocreatine, choline-containing compounds , lactate and N-acetyl-aspartate(NAA) containing compounds. Decreased NAA(neuronal loss) ,increased choline(cell membrane disruption) ,decreased NAA/Cr ratio etc. is commonly found in coma or vegetative state.(21)

4.10.3.ELECTROPHYSIOLOGY

For the assessment and follow up study of the patients in VS and MCS, the neuro physiological studies play a crucial role. They include EEG(Electroencephalogram) and EP (Evoked potential) studies like SSEP(Somato sensory evoked potential), VEP(Visual evoked potential) and BERA(Brain stem evoked auditory response).(23)

a.EEG(Electroencephalogram)

EEG assesses and records the electrical activity in brain. The normal brain activity or the awake pattern will be recorded as alpha or beta waves. Seizure activity in brain will display epileptiform waves. Slow wave dysfunction in the form of delta or theta waves will be seen in patients with disorders of consciousness. (24)

Detection of Gamma Band Oscillations (GBO) in EEG is a recent study which indicates cortical neuronal activity. Thus increased GBO shows improvement in consciousness and wakefulness. GBO in BFPV (Basal forebrain parvalbumin)

neurons is considered as a target of stimulation in diseases like vegetative state.(25)

EEG in vegetative state

Patients in VS show slow wave dysfunction pattern which constitutes delta and theta waves, which occur in 4-7.5Hz (theta) and 1-3.5 Hz (delta) frequency ranges .Reappearance of alpha waves instead of delta and theta wave patterns can be associated with clinical recovery.(24)

EEG in the minimally conscious state

Type and area of cerebral lesion influences the EEG wave pattern in MCS patients. Slow wave dysfunction can be focal or diffuse and can be of delta or theta type.(24)

b. Evoked potential studies

In brain injury, the evoked potential studies can be normal, delayed or absent. Studies have shown that disorders of consciousness are usually associated with delayed response and if absent, that is suggestive of poor prognosis. (24)

Somatosensory evoked potentials (SSEPs)

Stimulation of afferent peripheral nerve fibers results in the generation of impulse in the sensory cortical brain area. The impulse provided from this can be a square wave pattern of 0.2-2 milliseconds.

The usual sites for SEP stimulation are where the nerves are superficial compared to the other areas. These areas include the posterior tibial nerve at the ankle, the median nerve at the wrist and the common peroneal nerve below the knee.

Reference scores for latencies and inter peak latencies are established by each neurophysiology laboratory separately. The values for latency will differ

depending on the height and weight of the patient. Responses recorded are classified based on specific latencies.

SSEPs obtained in response to median nerve stimulation will be delayed and attenuated in patients with disorders of consciousness. Absence of the N 20 cortical response can be seen in VS and MCS patients.(26)(27)
Cortical responses are better indices of cerebral injury when compared to spinal responses , to predict the recovery and prognosis after severe brain injury because spinal components can be normal in latency and amplitude among the patients with DOC.(24)

BERA (Brain Stem evoked auditory response) and VEP (Visual evoked potentials)

BERA and VEP can be normal, delayed, diminished or absent in VS patients. This will depend on the severity and areas of brain involved.
Damage in the pons and mid brain can be detected as abnormality in 3rd and 5th wave patterns in BERA.(24)(26)(28)Auditory and visual areas if found to be preserved, stimulation of these areas in particular may augment recovery from coma/vegetative status by forming circuitry/ neural synaptic connection with arousal/awakening centers in the brain.

N9	Erb's point
P14	caudal medial lemniscus
N20	Thalamocortical radiations.

Table4.2. *Wave forms and areas of representation in Evoked Potential studies(29)*

Variation in conduction velocity (latency) can be assessed from the N9, P14, and N 20 measurements. Time for conduction between the brachial plexus and cervical spine can be calculated from the interval between N9 and P14. Similarly lag between brain and cervical spine can be obtained from P14 to N 20 interval. This is called the brain conduction time (BCT).(29)

P14 HAS A PREDICTIVE VALUE

As P14 latency is associated with cord dysfunction, prognosis can be worse or quite unlikely if it is significantly prolonged or absent.

4.11 INTERVENTIONS FOR PATIENTS WITH DISORDERS OF CONSCIOUSNESS

Major treatment modalities explained in the literature for the treatment of disorders of consciousness include pharmacological interventions, direct neural stimulation ,(electrical stimulation, magnetic stimulation etc.) , multisensory stimulation methods etc.

4.11.1 PHARMACOLOGICAL AGENTS FOR PROMOTING WAKEFULNESS/ AROUSAL

Various medications have been tried to improve arousal in patients with DOC. (4)

The following group of medications have been tried to improve arousal.

a. Dopaminergic Agents(30)

One of the commonly prescribed medications during the acute period of brain injury is Amantadine. It is mainly used in the treatment of Parkinsonism and also as an antiviral agent.(31)

b. Syndopa (or Levodopa)

Although an antiparkinsonian drug , its use in disorders of consciousness has been studied previously and published. The effect of this drug in vegetative or minimally conscious state is depends on the pathophysiology of the disease and the response to the drugs may vary.(32)(33)

c.Modafinil(34)

This is considered as a neuro stimulatory drug mainly used for the treatment of increased daytime somnolence associated with narcolepsy. According to the previous studies improvement can be seen in attention span, behavioural and cognitive responses for patients who receive modafinil.(35)

d.Zolpidem(36)

Zolpidem is a GABA agonistic drug which is commonly used to induce sleep with less side effect of day time somnolence. In various disorders of consciousness, Zolpidem is tried as an "awakening' agent. The rationale has been suggested to be diaschisis. (20)

e. Amphetamines

Amphetamine belongs to neuro stimulant group of drugs. Studies shows that it can be beneficial it treating conditions like depression, bipolar disorders, and disorders of consciousness. The major mechanism of action explained is the increase in level of Dopa which is a stimulatory neurotransmitter.(37)(38)

4.11.2 SENSORY STIMULATION

The concept of various stimulation programmes for the patients with disorders of consciousness has been introduced earlier. It has been suggested that when the environmental stimulation programmes are provided at a defined intensity,

duration and frequency, it can definitely influence the speed of recovery from disorders of consciousness to a great degree. They also stated that “in comatose patients, although the problem is primarily cerebral, there is a condition of environmental deprivation that could lead to widespread impairment of intellectual and perceptual processes accompanied by changes in cerebral electrical activity”.(39)

Repeated use and response to environmental stimuli are the major ways through which development of new neural circuits occur in the brain. This is the reason why scientists suggest multiple sensory stimulation modalities as part of coma stimulation programme. These include auditory , visual, tactile stimulation etc.

Oral feeding is one such stimulation modality. As the patient watches the spoon approach, an anticipatory mouth opening response can be elicited. (6)

4.11.3. ELECTRICAL BRAIN STIMULATION

Electrical brain stimulation (EBS) which is otherwise known as focal brain stimulation (FBS), is a technique basically used in research. Neuronal stimulation and there by cell membrane excitation occurs by the application of electric current.

Localization of functions in the brain areas and electrical excitability of nerves and muscles are the two major rationale of electrical stimulation. This microstimulation will result in the activation of neurons around the stimulating electrodes. This can happen even at a low amplitude current of 10µA.

Examples of therapeutic EBS are Deep brain stimulation (DBS), Transcranial direct current stimulation (tDCS), Central thalamic deep brain stimulation (CT-DBS), Functional electrical stimulation (FES), Deep transcranial magnetic stimulation (Deep TMS) etc. (40)

a. Transcranial direct current stimulation- tDCS

Studies show that transcranial electric current stimulation can bring improvement in the consciousness status of DOC patients. A study conducted among MCS patients showed increment in the assessment scales as the stimulation was performed. It was an immediate behavioural response. Some patients were given tDCS three months later and further improvement in recovery scores was noted.

Patients in PVS did not show immediate improvement in consciousness state after tDCS. A patient who was in a PVS six years down the line was given tDCS. He showed improvement in the follow up visits and later it was reported that he improved to MCS. Studies show that improvement in the consciousness status with tDCS is related to the duration and severity of brain injury. (41)

b.Central thalamic deep brain stimulation(DBS)

Studies for the improvement of consciousness status in patients with severe traumatic brain injury using DBS show that this modality may improve the behavioural functions and responses of the patients with DOC. Central thalamus is a crucial area in the brain where attention , motor, and memory functions are controlled and augmented. Thus stimulation of this area can result in the improvement of attention and motor response functions. Further studies are needed in this area as the results remain mostly theoretical and experimental. (42)

c.Transcranial magnetic stimulation in disorders of consciousness.

Transcranial magnetic stimulation provides non-invasive stimulation of neuronal cells and its use in patients with disorder of consciousness is under

study. Adjusting the magnetic power in units of Tesla, different depths of stimulation is achieved.(43)

4.11.4 DORSAL COLUMN SPINAL CORD STIMULATION (DCS)

DCS (dorsal column stimulation) is found to be useful for the improvement of clinical symptoms in disorders of consciousness. Studies have shown that DCS causes increased cerebral blood flow, increase in the level of stimulatory neuronal transmitters and improvement of the wave patterns in EEG. (44)

4.11.5. PERIPHERAL NERVE STIMULATION FOR DISORDERS OF CONSCIOUSNESS

Here peripheral nerves are used as the portal of supply of electrical impulses to the central nervous system. The rationale for using peripheral nerve stimulation for DOC is the neuroplasticity. This occurs due to the modulation of neural activity with the electrical impulses that reach the central nervous system through peripheral nerves. The effect of stimulation will be influenced by various factors like severity and duration of brain injury and stimulation parameters used for the therapy. (45)

4.12.RIGHT MEDIAN NERVE STIMULATION(RMNS)

The usefulness of right median nerve stimulation to promote wakefulness in patients in vegetative state has been a subject of research in the last two decades. In median nerve electrical stimulation, surface electrodes are placed at the wrist as median nerve is more superficial here. (46)

Functional magnetic resonance imaging (fMRI) was used as an assessment tool in one of the previous studies using RMNS patients with disorder of consciousness. This was to analyse the brain activation that happens on

electrical median nerve stimulation. Somatosensory cortical system was activated by median nerve electrical stimulation and this was analysed using fMRI.(47)

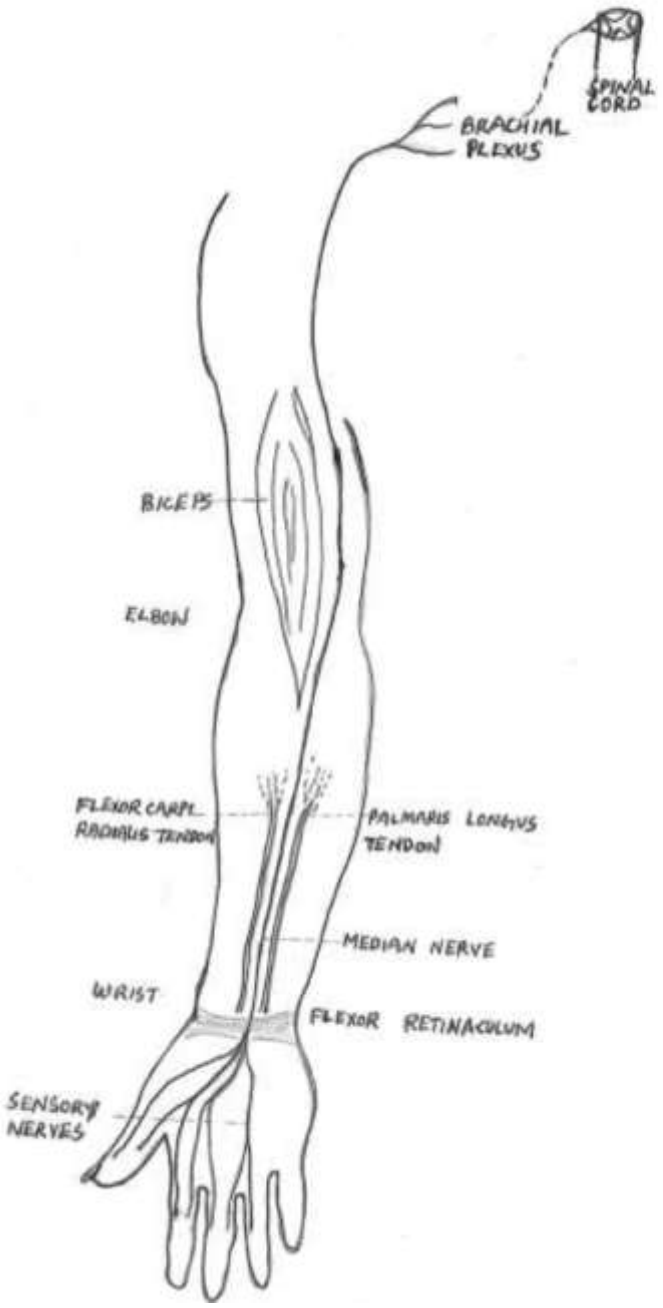


Figure 4.3: Anatomical course of the median nerve through the upper limb.(46)

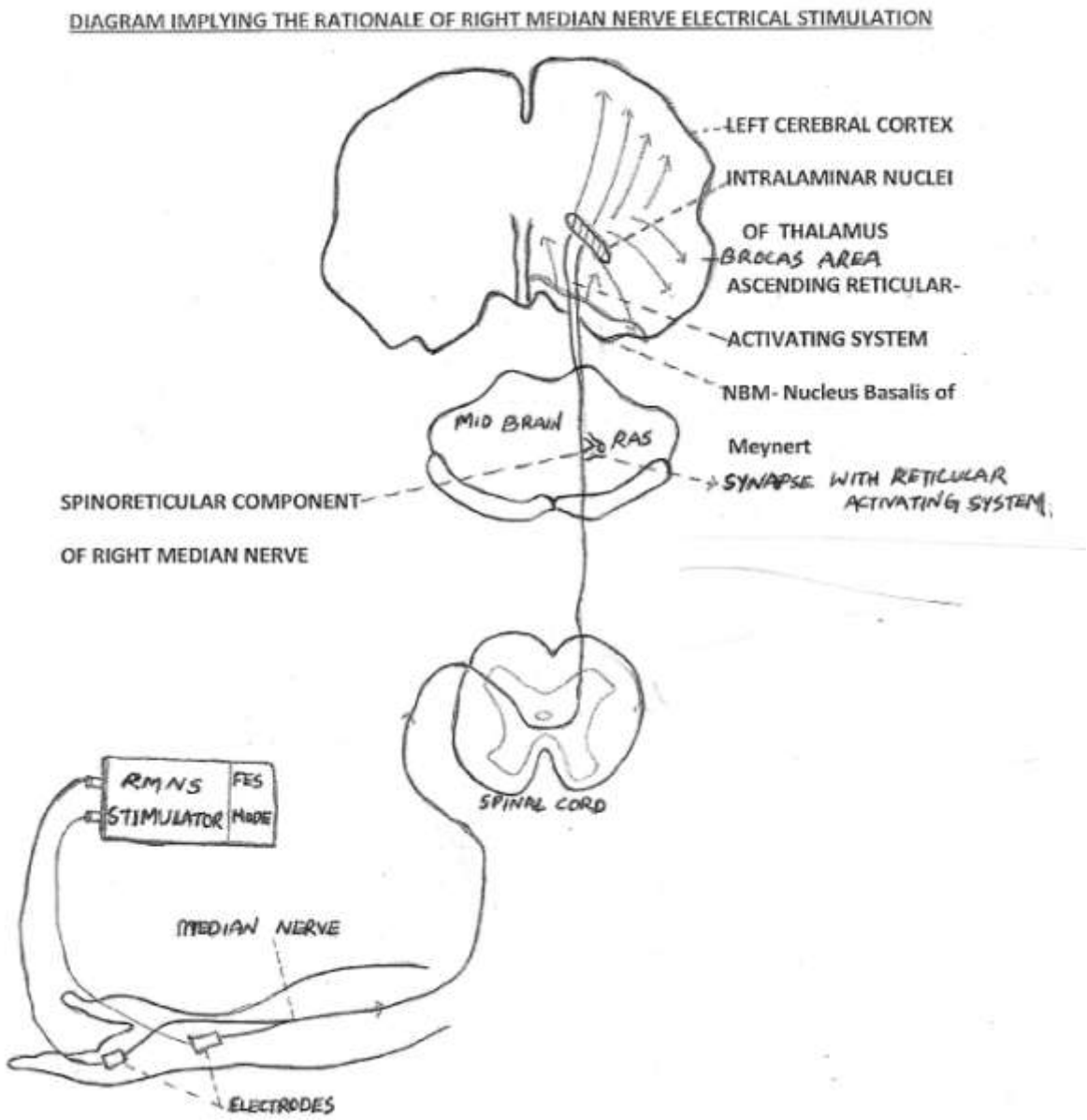


Figure 4.4. Diagram showing pathway of Median nerve stimulation and its mechanism.

4.12.1 Rationale of right median nerve stimulation

Almost 2 decades ago, Tetsuo Kano in Japan and Dr.Cooper in U.S, independently noted the ability of electrical stimulation to increase the level of consciousness. In their study electrical stimulation was being used for reducing spasticity. Following this clinical observation, Kano and Cooper initiated the research to use electrical stimulation for arousing the central nervous system.

They tried to utilise its effect for the improvement of patients with disorders of consciousness like coma and vegetative state.

The right median nerve can act as a peripheral portal of entry of electrical impulses to the central nervous system. This port can be used to deliver stimulatory electrical impulses to the centre of arousal. Compared to other parts of body, sensory representation of the hand in the cerebral cortex is disproportionately large.

Centre of arousal and wakefulness is situated in the brain stem. The neural network associated with the function of wakefulness is the ascending reticular activating system (ARAS). ARAS is in synaptic connection with the spinoreticular component of the median nerve pathway. (48) The ARAS originates from pons, which in turn is related to the centres where noradrenergic and serotoninergic neurotransmitter systems originate.(49) There is a functional relation between the ARAS (centre of arousal) and the NBM (Nucleus Basalis of Meynert) which is one of the centres of the cholinergic system. Origin of cholinergic system in the cortical region is at NBM. It is important for maintaining the cortical activity needed for wakefulness. The cholinergic system in brain also plays a crucial role in the process of memory and other cognitive functions. It is proposed that right median nerve electrical stimulation has a significant effect on NBM and thus can bring increased cortical activity in patients with disorder of consciousness. (50)

Studies state that nor epinephrine and dopamine are stimulatory neurotransmitters, the elevation of the levels of which can result in the improvement of level of consciousness. Thus electrically induced elevation of these stimulatory neurotransmitters can be used as a modality to increase the awareness and wakefulness of patients in acute coma, or in chronic vegetative

or minimally conscious states. The elevation of these transmitters can also result in increase in cerebral blood flow which can further bring augmentation in cerebral cortical activity. This is measurable with studies like Doppler analysis and this is observed quite shortly after starting the right median nerve stimulation(MNS). (51)(49) (52)

Broca's motor/speech planning area is located in the left frontotemporal region in majority of persons , no matter whether they are right handed or left handed. When a subject moves his hand, Broca's area becomes more active and increase in this cortical activity can be detected by brain imaging studies like PET. Studies show that the above mentioned process can be artificially driven by RMNS. (3)

Another mechanism by which the peripheral nerve electrical stimulation brings augmentation of neuronal activity is by elevation in the cortical levels of neurotrophic factors like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). Neurotrophic factors play an important role in neuroplasticity. This is by the transformation of silent synapses into functional ones.(53) There is one study which shows increase in BDNF levels in rats brain with a transient global ischemia, when they were given electrical neural stimulation. These findings prompted scientists to utilise peripheral electrical stimulation as a modality to increase neurotrophic factors which can eventually lead to the improvement in the consciousness level of patients with disorder of consciousness. (54)

Improvement in EEG and increase in cerebral blood flow with a more active metabolism of catecholamines as measured by SPECT has been seen in RMNS study group patients. (55)

The key message by Prof Cooper is the fact that "awakening is the result of accurate repetition many thousands of times that tells the brain and spinal cord – wake-up, wake-up, wake- up, wake-up, wake-up ….". It is stated in their study analysis that as the patient receives 10 million pulses in the10-week protocol of median nerve stimulation, it is like telling someone to wake up 10 million times. (55)

4.12.2. CLINICAL OBSERVATIONS AFTER RIGHT MEDIAN NERVE STIMULATION IN COOPER'S STUDY:(3)(1)

When the right hand is being stimulated, mirror movements may be seen in left hand in the initial days of treatment. This indicates that an active neuronal cross over activity is occurring through the corpus callosum which results in the reactivation of the cortical circuits in both cerebral hemispheres. A vague opposition movement of right index finger and thumb may be the initial simple one step command that the patient may show after one or two weeks of RMNS therapy.

"This purposeful right hand response while the brain injured patient still appears to be semi-comatose, demonstrates that the five million electrical pulses delivered to the nervous system in the first 10 days of treatment have been copied and stored in the hard drive of the brain (Cooper &Kano, in press)."

During the stimulation there can be involuntary contraction of the flexor muscles of forearm which are innervated by median nerve. During stimulation thumb may repeatedly abduct and flex whereas the index and middle fingers may be in flexion/ relaxation. There may be subtle flexion movements of the wrist joint. Minor contractions may be noticed in the left thumb.

There can be improvement in head control and trunk control in the subsequent period as the depth of coma and vegetative state gets better. Increased skin circulation and salivation is also noticed in the initial weeks of therapy. Facial expressions of comfort or discomfort may also be noticed in the later period. Groans and phonation can follow these clinical observations. Semi-purposeful hand movements may be observed in the subsequent stages. It is stated in Cooper's observations of RMNS therapy that there can be even full awakening to a conscious level.

There is considerable interpersonal variability that exists in the regaining of behavioural function, speech and cognitive abilities and ambulatory functions after the initial stages of responses. Oral reflexive movements and swallow function may be regained as the patient awakens from coma. But he or she will be fully dependent for feeding. If improvements in the neurological function continues, the patient may show ability to talk and walk subsequently.(3)

4.12.3. PREVIOUS STUDIES WITH USE OF RIGHT MEDIAN NERVE ELECTRICAL STIMULATION TO IMPROVE AROUSAL IN PATIENTS WITH DOC

The idea was first conceptualised in 1994 by a scientist named Suzuki, following which pilot studies were done by Yokohama, Mohuja and Cooper et al, the details of which are not available.

The first published study was in 2001. It was a pilot study in a few comatose severe brain injured patients. Sample size was small and even though there was clinical improvement, statistical significance could not be seen. (56)

The same group repeated the study in 2003 on three decerebrate comatose patients and suggested that it was found to be beneficial for regaining consciousness. Synaptogenesis in the damaged cerebral cortex and stimulation of the Brocas' motor speech area with RMNS was suggested as a possible

mechanism then. But they couldn't ascertain this and explain the proper mechanism for increased wakefulness.(57)

In 2005 Cooper et al. reviewed studies on electrical stimulation in patients with Alzheimer's disease and disorder of consciousness in the previous two decades. They also studied the effects of right median nerve electrical stimulation in patients with severe traumatic brain injury. The study was conducted among two patients who were in the acute period of trauma and one patient who was in the sub acute phase of brain injury. They commented that improvement in consciousness status may be possible with the stimulation even in patients with chronic traumatic brain injury.(3)

In 2013 a study was conducted among patients with diffuse axonal injury who were in vegetative state. Along with structured multi sensory coma stimulation program, median nerve electrical stimulation was also given to these patients. This study was conducted in a case control manner and they state that significant difference in the consciousness level was observed in patients who received additional median nerve stimulation therapy. Suggestions from this study included a larger sample population based on severity of injury, level of consciousness as to whether the patient is in vegetative state or minimally conscious state, age, duration of coma as well as longer follow-up to assess the improvement in the neuro behavioural functions(58)

A still recent study used positron emission tomography (PET) in addition to clinical scales, to identify the changes in brain metabolism following RMNS therapy in patients with DOC. They concluded that RMNS is a safe, non-invasive therapy and may bring improvement in the level of consciousness in patients with brain injury. They state that RMNS does not have any reported side effects and this stimulation modality can be used for all patients who are in disordered consciousness states like coma or vegetative state.(2)

4.12.4. SCOPE OF NEW STUDY

Median nerve Stimulation provides a cost effective treatment that can be tried to improve arousal in patients with disorders of consciousness along with other modalities. All the former studies calls forth continued research in this field and they point out the need to perform the study among a larger series of sham/treated comatose patients to prove the effect of right median nerve electrical stimulation for improving the consciousness status of the patients with brain injury.(3)

The challenge of exploring median nerve stimulation was summarised by Professor John Jane, a medical person with a vast experience in the field of neurotrauma and the chairman of Department of Neurological Surgery and University of Virginia as:

"Very few things do work in this situation and if your techniques make any difference whatsoever, I think it would be well worth it." (3)

"Concluding with the words of Shakespeare in Hamlet:

"Diseases desperate grown
By desperate appliance are relieved,
Or not at all."

(Hamlet, Act IV, Scene III)"

5. METHODOLOGY

5.1 Study design

Randomized controlled double blind trial

5.2 Settings and location where the study was conducted

Department of Physical Medicine and Rehabilitation, Christian Medical College, Vellore.

Patients were recruited from the inpatient wards under the Department of Physical Medicine and Rehabilitation in Christian Medical College Hospital, Vellore and the Rehabilitation Institute. Those who satisfied the inclusion criteria were explained about the study and informed consent in their own language was obtained from the relatives of the patients who were willing to participate. These patients were then randomly allocated into 2 groups- the experimental group receiving electrical stimulation of the median nerve and the control group receiving sham stimulation. Pre and post intervention, both groups of patients were assessed using outcome measures by the primary investigator who was blinded as to which group the patient was allotted to.

EEG analysis which is one of the secondary outcome measures was done in the Neuro Electrophysiology lab of the Department of Neurology, CMC Vellore.

5.3 Ethics committee approval

Approval for the study was obtained from the Institutional Review Board (Annexure)

The consent form was submitted in four different languages as expected in the population group (English language version given in Annexure)

5.4 Participants

Inclusion criteria

1. Patients in vegetative or minimally conscious states following acquired brain injury

2. Age: 18-70 years

3. Duration of injury less than one and a half years.

Exclusion criteria

1. Patients with injury of the right brachial plexus or median nerve

2. Patients with fracture of the right wrist

3. Pregnancy

4. Patients with cardiac pacemaker

5. Patients with metallic implant in the right upper limb

6. Patients in locked in syndrome/akinetic mutism/abulia

7. Patients with cervical spinal cord injury

5.5 Sample size

32 patients (16 each in experimental and control group) in vegetative or minimally conscious states between the ages of 18-70 years were targeted for selection from the inpatient wards in the PMR department.

Method of sample size calculation:

Based on means and standard deviation sample size was calculated using the equation

EQUATION 5.1 - SAMPLE SIZE CALCULATION

$N=2SD^2\times (Z\alpha+Z\beta)^2/ (\mu1-\mu2)^2$

Where N=sample size in one arm of a randomized control trial

SD=standard deviation=2

Z α=1.96

Z β=0.84

$\mu1$=mean of score with standard therapy alone

$\mu2$=mean of score with standard therapy combined with RMNS

$\mu1 - \mu2 =2$,

Thus putting the values in the equation

$2\times2^2\times (1.96+0.84)^2/2^2$

=16

Thus required sample size in each arm=16 and total sample size calculated is 32.

5.6 Randomization

5.6.1 Method of allocation concealment

Serially labelled opaque envelopes concealed randomised allocation.

5.6.2 Method of randomisation

Randomization was done using computer generated random numbers. Variable block size of 2 and 4 were used. Accordingly, 16 patients were allocated to the experimental group and 16 patients to the control group by the occupational therapist in charge of the patient.

5.6.3 Blinding

The primary investigator assessing outcome and the patients' care takers were blinded to the intervention. For the sham group the electrodes were placed in the same manner as the stimulation group, without increasing the intensity of the current.

5.7 Implementation

Patients were recruited from PMR wards of CMC hospital and Rehabilitation Institute. Those who satisfied the inclusion criteria were explained about the study and informed consent in their own language was obtained from those who were willing to participate. Patients were then randomly allocated into the two groups. Right median nerve stimulation was given to the experimental group and sham stimulation to the control group as described below. Both groups received the standard coma stimulation program. Pre and post therapy assessments with primary and secondary outcome measures described below were done by the primary investigator who was blinded to the intervention. Statistical analysis of the results from both groups was done to look for any statistically significant difference in the scores

5.8.1 Intervention group

In the experimental group, stimulation was done with Functional Electrical Stimulator (FES) designed by the Department of Bioengineering, The FES is used in the Occupational Therapy section for electrical stimulation of muscles in patients with stroke, spinal cord injury etc, usually to improve muscle strength and reduce spasticity.

The following were the settings used for stimulation of the median nerve.
Frequency= 40 Hz; Current=20mAmps; Pulse width=300μsec; on duration=20sec/min

Electrodes were placed at the volar aspect of right hand wrist such that cathode is 2 cm proximal to palmar crease and anode is 2 cm distal to palmar crease'. Stimulation was done for one hour each in the morning and afternoon sessions for a total of forty sessions over a period of four weeks.

Figure 5.1. FES pocket stimulator

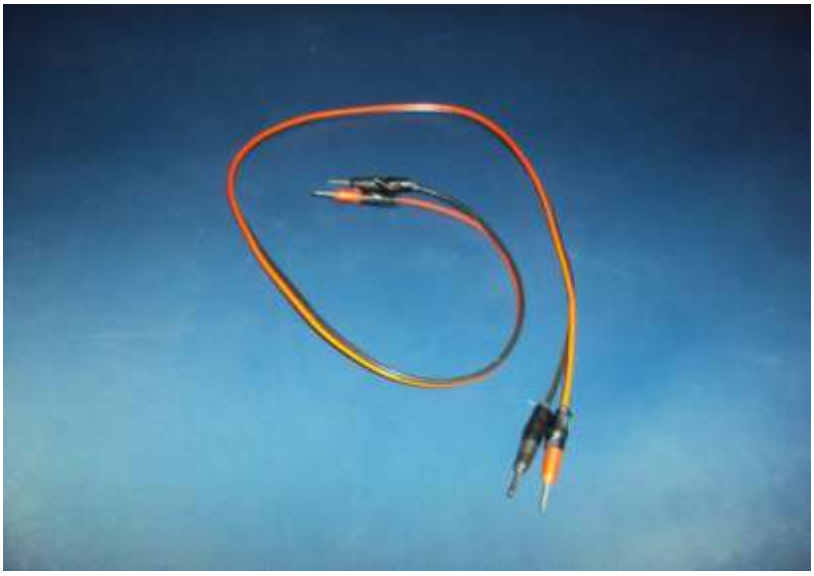


Figure 5.2: Wires used for FES

Figure 5.3. FES adaptor with four rechargeable batteries

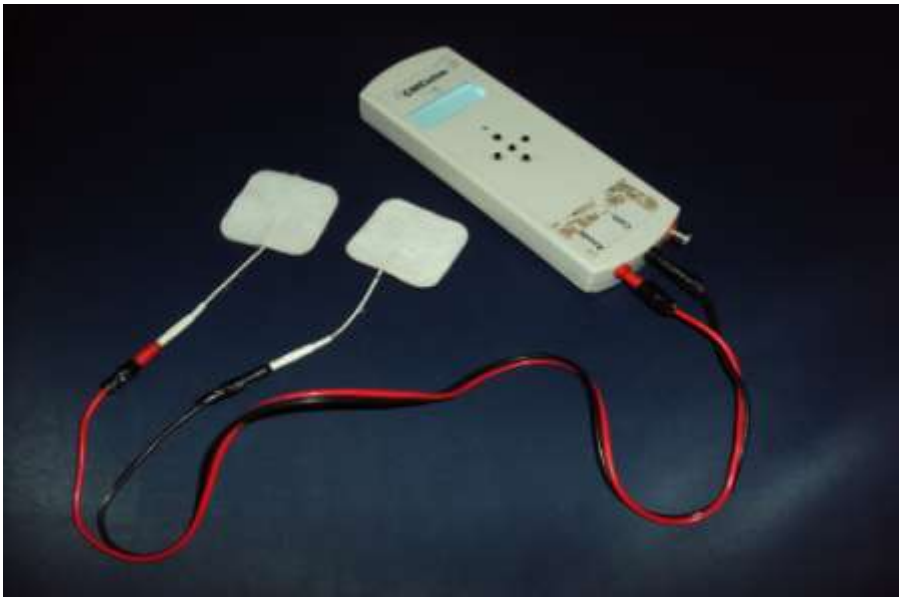


Figure 5.4. FES pocket stimulator connected with wires and surface gel electrodes ready for stimulation.

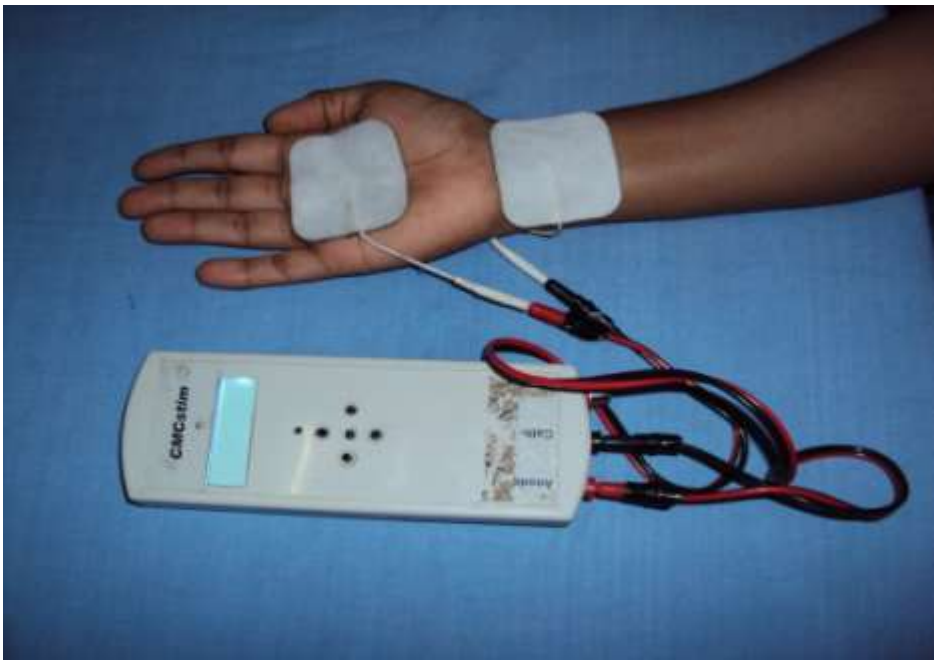


Figure 5.5. Position of gel electrodes, cathode proximal and anode distal in the wrist region for stimulating median nerve.

FES pocket stimulator has four basic settings in which the second one which is the FES mode is the one used for RMNS therapy.

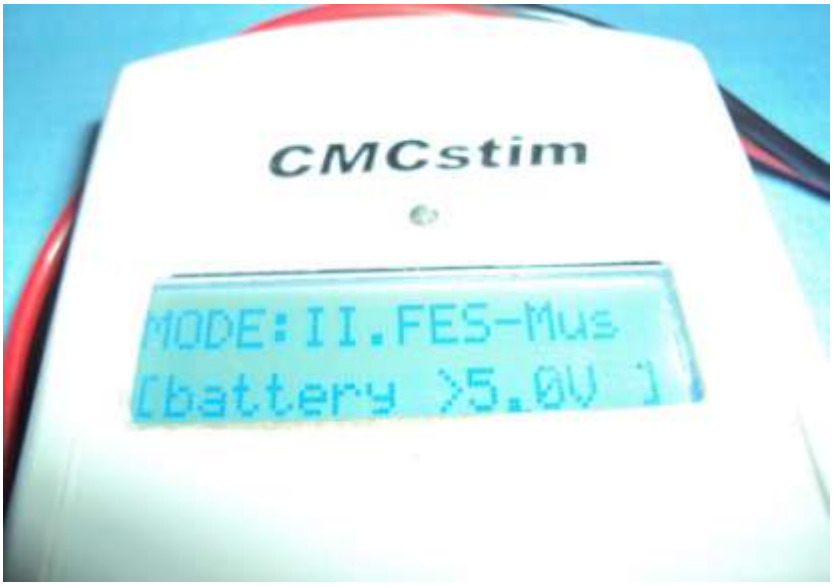


Figure 5.6. FES pocket stimulator in the FES mode, (which is set in it as mode ii)

5.8.2 Control group

The control group received sham stimulation. In this group, the electrodes were placed in the same manner as the stimulation group without increasing the intensity of current.

5.9 Outcome measures

The following were the primary and secondary outcomes assessed pre and post intervention.

5.9.1 Primary outcome measures

1. CRS-R (Coma Recovery Scale Revised)
2. WHIM Score (Wessex Head Injury Matrix score)
3. RLAS (Ranchos Los Amigos Scale)
4. GOSE (Glasgow Outcome Scale Extended)

1. Coma Recovery Scale Revised (CRSR)

(Published in 2004 from Johnson Rehabilitation Institution, Centre for Head Injuries, New Jersey)

It has six sub scales with a maximum score of 23. The sub scales are auditory scale, arousal scale, communication scale, motor function scale, oromotor scale and visual function scale.

2. Wessex Head Injury Matrix (WHIM)

This scale has 62 different hierarchically arranged score points for the assessment of recovery from coma. There is good interrater agreement for this scoring system. This scale also exhibits very good test-retest reliability. For the detection of subtle changes in the response status that is happening during the recovery WHIM is better compared to GCS scoring system, which is commonly used in acute injury scenario.

3. Rancho Los Amigos Scale (RLAS)

This scale assesses how much the patient is aware and cognitively sound to respond to stimuli from external environment. Although it is frequently used for patients with trauma, as it is a cognitive functioning scale here it is used to get a gradation of the cognitive and behavioural responses as they improve in the consciousness status. Based on their cognitive and response status the patients with DOC are given scores (1-8). Each of the eight levels represents the typical sequential progression of recovery from brain damage. Score 1 indicates cognitive function with absent response and score 8 represents appropriate and purposeful functioning. Here Level 1 almost corresponds to coma, Level 2 corresponds to vegetative state showing some reflexes without awareness and Level 3 corresponds to minimally conscious state with some amount of awareness.

4. Glasgow Outcome Scale Extended (GOSE)

This can be considered mainly as a social scale which assesses the dependence status of patients as they recover from coma to a conscious level. This is mainly used here to assess the recovery of those patients who has shown considerable improvement in the level of consciousness and behavioural response status. According to GOSE scale, level 2 is Vegetative state (VS). That indicates absence of cerebral cortical function that can be assessed and judged by a behavioural response. Here Level 3 (Lower severe disability) indicates that the patient needs full assistance in ADL throughout the day, which almost corresponds to minimally conscious state.

5.9.2 Secondary outcome measure

Electroencephalogram (EEG) was done as a secondary outcome measure to assess changes in brain electrical activity by analyzing the variation in the pattern
of waves. Alpha waves replacing the pathological theta and delta waves has been proposed as a possible change occurring during recovery. EEG analysis was done in the Neuro Electrophysiology lab of the Department of Neurology, CMC Vellore.

5.10 Statistical analysis

All comparisons between the groups were analyzed using Mann Whitney U test. Kruskall Wallis test was also used to test the association between the variables of more than 2 categories and the outcome variable (difference in pre and post scores). This test was chosen for significance with 2 tails. To declare a test statistically significant, a level of 5% was used. The statistical software used for analysis was STATA 13.0.

6.RESULTS

26 patients who fulfilled the inclusion criteria were enrolled into the study. These patients were then randomly allocated into two groups-the experimental group and the control group. Two patients dropped out from the experimental group. Thus the total number of patients who completed the study was 24, i.e. 11 in the experimental group and 13 in the control group.

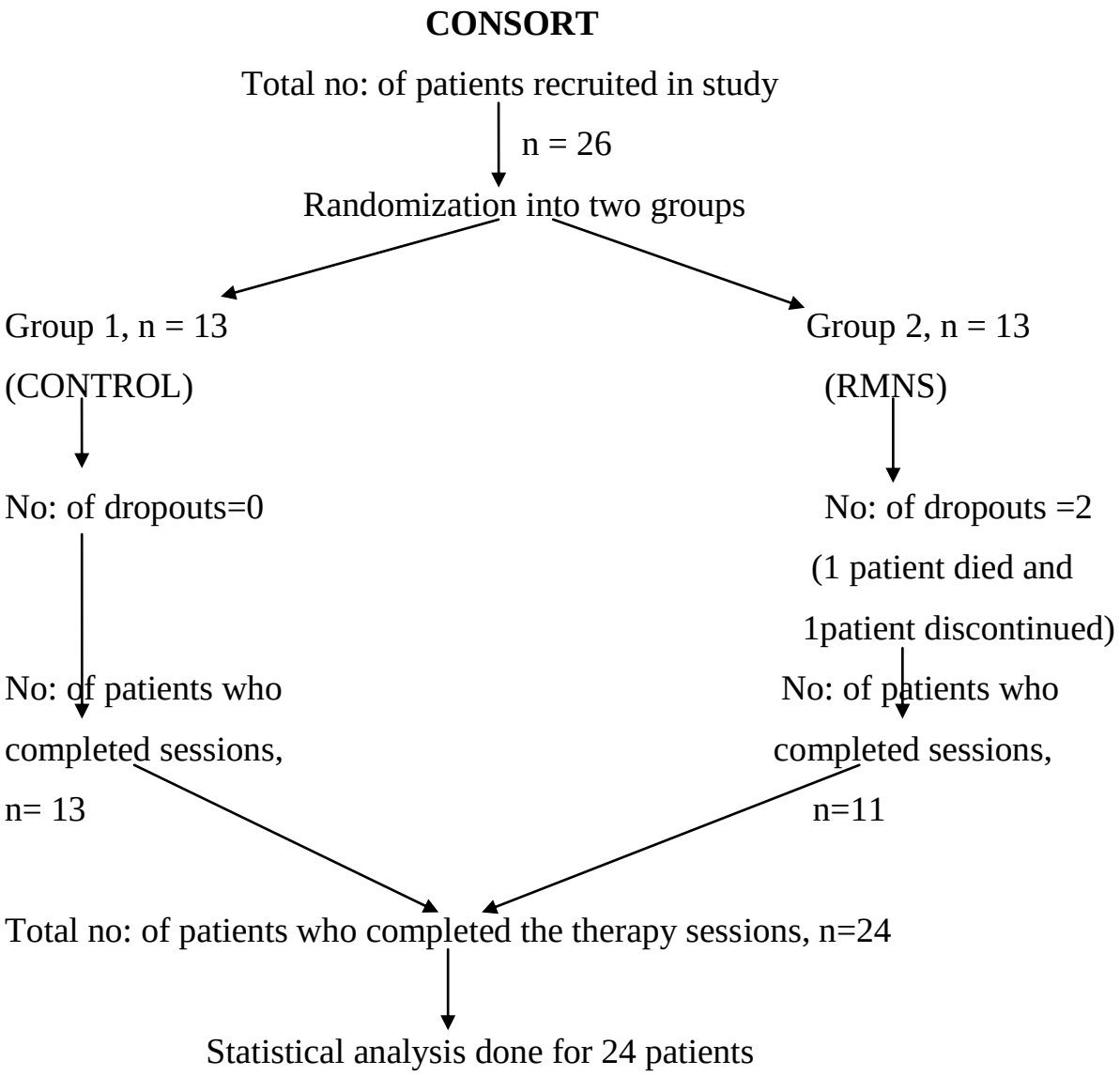


Figure 6.1 – Consort

6.1. DATA ANALYSIS

6.1.1. Demographic data of patients

Variables	Control	RMNS	Total	p-value (* -Fisher's exact)
Age				
18-29	4(30%)	4(31%)	8(31%)	
30-50	8(62%)	5(38%)	13(50%)	*0.35
>50	1(8%)	4(31%)	5(19%)	
Gender				
Males	8(62%)	10(77%)	18(70%)	
Females	5(38%)	3(23%)	8(30%)	0.39

Table 6.1 *Demographic data of patients*

a. Age: 50% of patients were in the middle age category. The mean age of the patients was 38.54 and its range was 19-59 years.

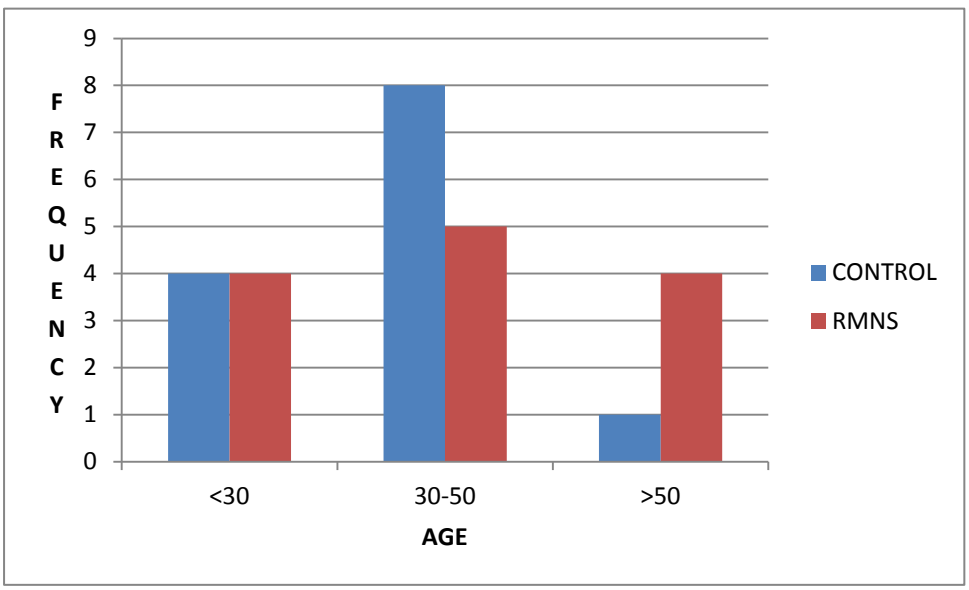


Figure 6.2.Age distribution of patients

b. Gender:

70% of patients recruited in the study were males, 77% in the experimental group and 62% in the control group.

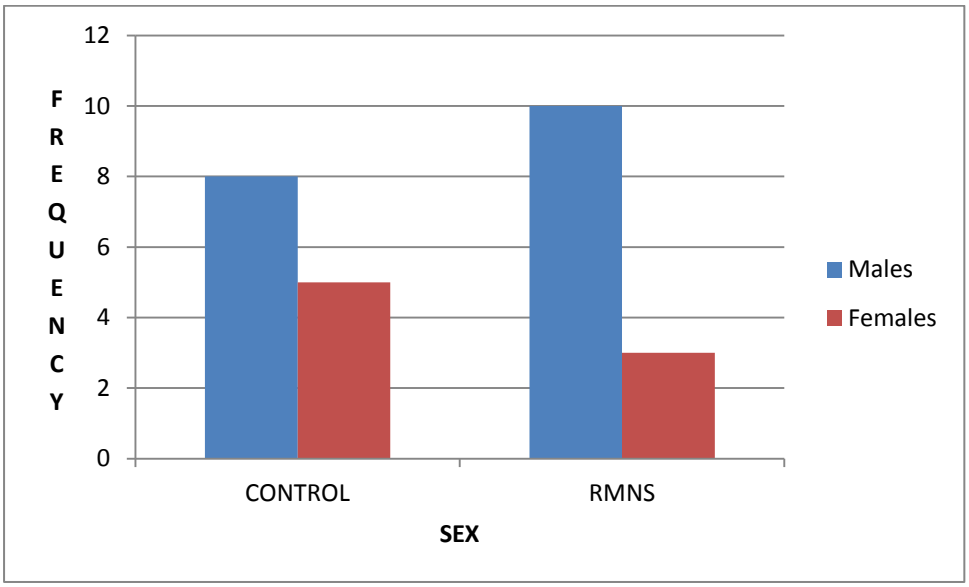


Figure 6.3. Gender distribution of patients

There was no statistically significant difference in the demographic data between the two groups.

6.1.2. Clinical features and management

	Control	RMNS	Total	Pvalue
Etiology of brain Injury				
Traumatic	11(85%)	10(77%)	21(81%)	
Non traumatic	2(15%)	2(15%)	4(15%)	0.99
Combined	0	1(8%)	1(4%)	
Duration of Injury				

<6months	10(77%)	8(62%)	18(70%)	
6months-1year	2(15%)	2(15%)	4(15%)	0.83
1 -1.5 years	1(8%)	3(23%)	4(15%)	
History of seizures				
Present	3(23%)	2(15%)	5(20%)	0.62
Absent	10(77%)	11(85%)	21(80%)	
Initial Level of Consciousness				
Vegetative	10(77%)	12(92%)	22(85%)	0.59
Minimally conscious state	3(23%)	1(8%)	4(15%)	
Abnormal Posture (decorticate/decerebrate posturing)				
Present	5(38%)	6(46%)	11(42%)	
Absent	3(24%)	4(31%)	7(27%)	0.78
Diffuse Axonal Injury				
Present	2(15%)	4(30%)	6(23%)	0.85
Absent	11(85%)	9(70%)	20(77%)	
Decompression Surgery				
Done	6(55%)	6(50%)	12(52%)	0.82
Not done	5(45%)	6(50%)	11(48%)	

Neurostimulant				
Given	10(77%)	5(42%)	15(60%)	0.07
Not given	3(23%)	7(58%)	10(40%)	

Table 6.2 *Clinical and radiological features and management of patients included in the study*

There was no statistically significant difference between the two groups in any of the variables studied.

a. Etiology of Brain Injury

Majority (81%) of the patients were in the vegetative or minimally conscious states secondary to traumatic brain injury while in the remaining, the etiology was non traumatic. One patient who was in the intervention group had combined injury because of cardiac arrest sustained after traumatic brain injury.

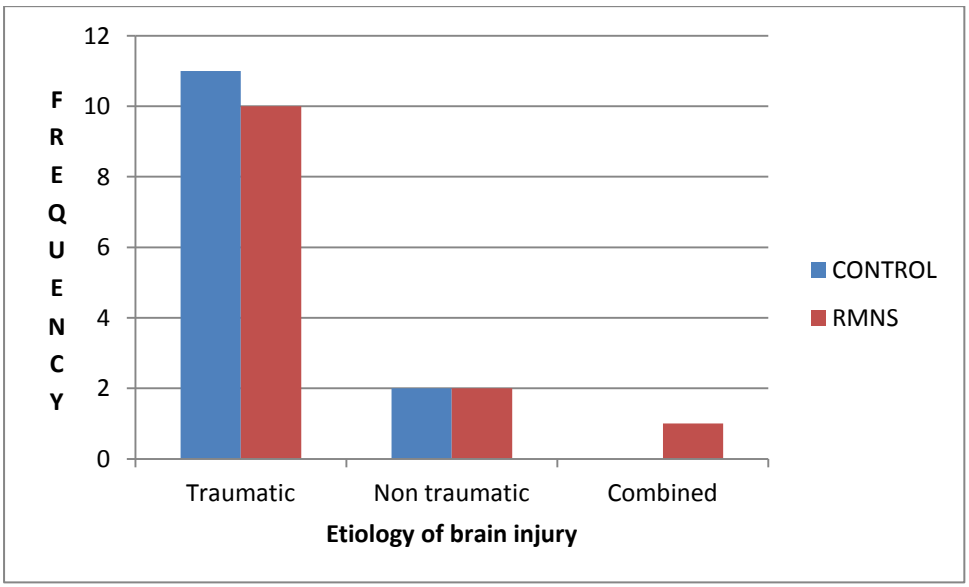


Figure 6.4. Etiology of brain injury

b. Duration of injury

77% of patients in the control group and 62% in the RMNS group had duration of injury less than 6 months. The mean duration of injury was 21.35 weeks and its range was 4-59 weeks.

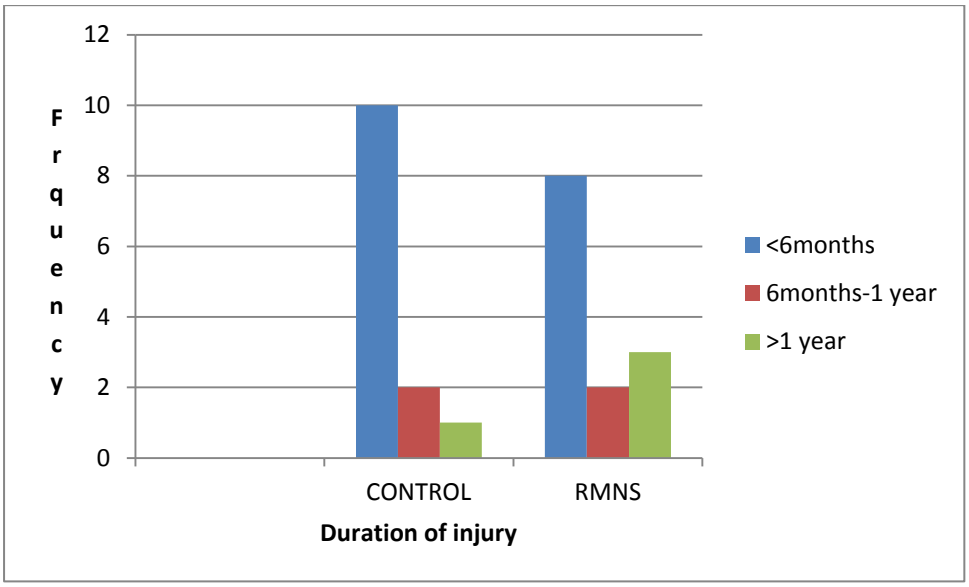


Figure 6.5. Distribution of patients according to duration of injury.

c. Initial consciousness status

Statistical analysis showed significance for the consciousness status at the time of recruitment with the outcome measures. Most of the patients (85%) were in vegetative state and 15% were in minimally conscious state at the time of enrolment.

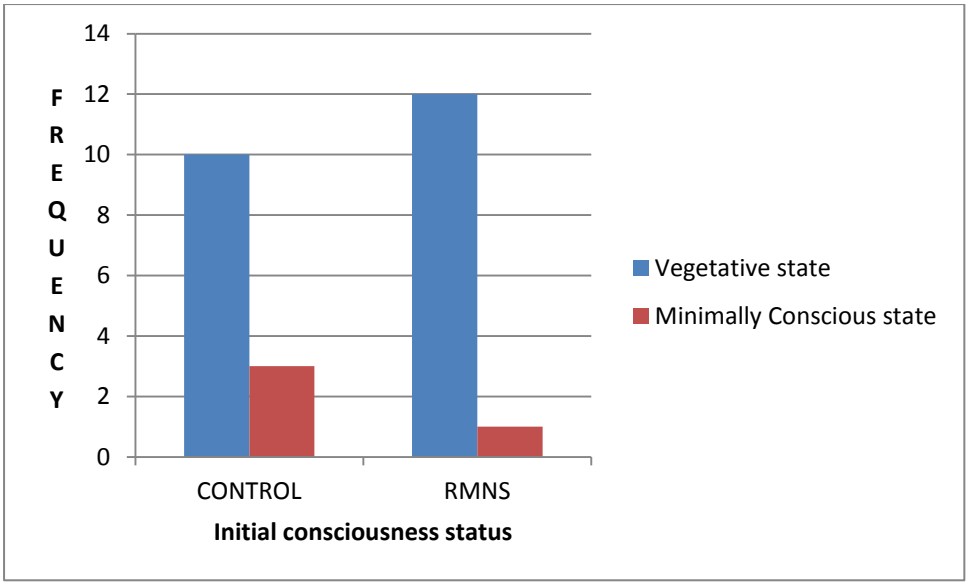


Figure 6.6: Distribution of patients according to the Initial Consciousness Status

d. Diffuse Axonal Injury(DAI)

Presence of diffuse axonal injury had a statistically significant association with the outcome measures. Distribution of DAI in the experimental and control groups were similar.

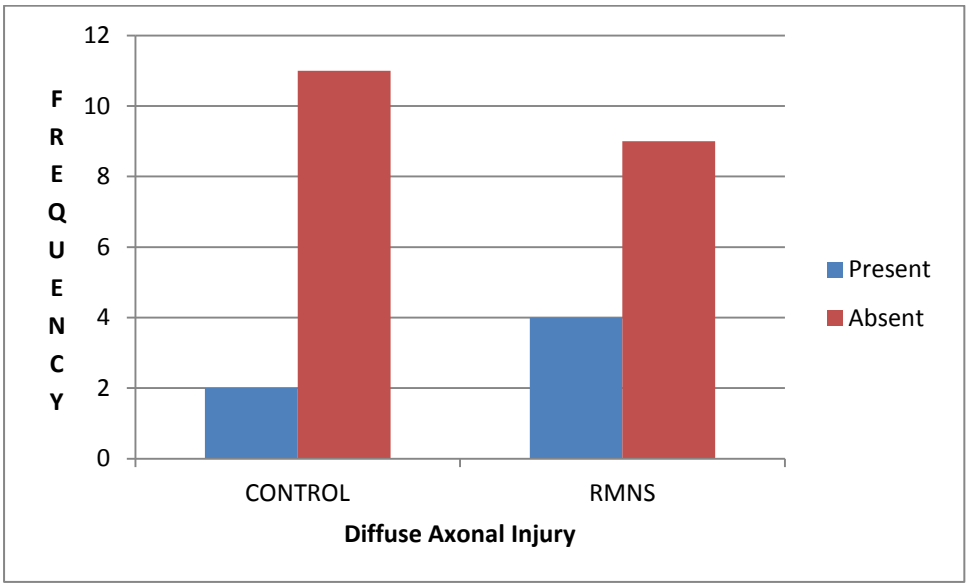


Figure 6.7. Distribution of patients according to the presence or absence of diffuse axonal injury.

6.1.3. Results of neurophysiological studies

	Control	RMNS	Total	p value
SSEP Median*				
Obtained	4(40%)	4(36%)	8(38%)	0.86
Not obtained	6(60%)	7(64%)	13(62%)	
P14 wave*				
Obtained	1(16%)	3(43%)	4(17%)	0.26
Not Obtained	5(84%)	4(57%)	9(38%)	
VEP*				
Obtained	8(73%)	8(80%)	16(76%)	0.70
Not Obtained	3(27%)	2(20%)	5(24%)	
BERA*				
Obtained	7(70%)	8(80%)	15(75%)	0.60
Not Obtained	3(30%)	2(20%)	5(25%)	

Table 6.3. *Results of Neurophysiologic studies*

*SSEP Median- Somato Sensory Evoked Potential from the cerebral cortex obtained through median nerve electrical stimulation

*P14 wave- Wave in SSEP study that indicates the intactness of the cervical cord

*VEP- Visual Evoked Potential

*BERA- Brainstem Evoked Auditory Response

SSEP wave forms were obtained on median nerve stimulation in 38% of the patients in whom the study was done while the Tibial SSEPs could not be obtained in any patient in whom the study was done. VEPs and BERA was obtained in 76% and 75% of the patients respectively. There was no statistical difference in the results of these studies between the 2 groups. Slow wave dysfunction was noted in the EEG in all patients prior to the intervention.

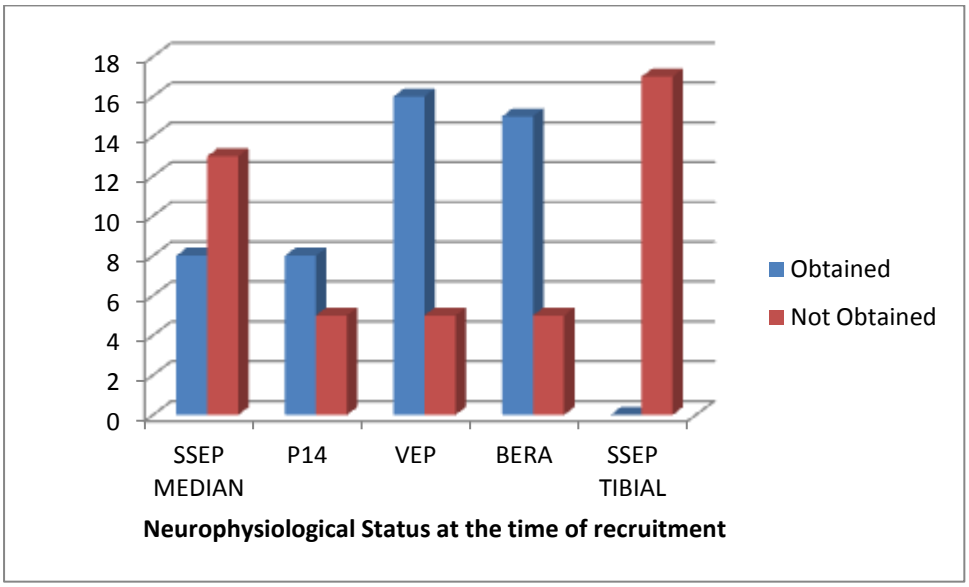


Figure 6.8. Results of electrophysiological studies at the time of recruitment.

6.2. OUTCOME MEASURES

6.2.1 Primary outcome measures

6.2.1.1 Analysis of *median values in pre & post therapy sessions* in both groups with various outcome scales

1= Pre therapy, 2= Post therapy

SCALE	CONTROL N=13 Median[Range]	RMNS N=11 Median[Range]	TOTAL N=24 Median[Range]	P-VALUE
CRS-R*				
1.	5[2-9]	6[2-9]	5[2-9]	0.57
2.	9[4-15]	11[5-23]	10[4-23]	
WHIM-MAX*				
1.	4[3-26]	3[3-21]	4[3-26]	0.68
2.	26[3-57]	16[7-53]	24[3-57]	
WHIM – TOTAL*				
1.	4[3-14]	3[2-12]	3[2-14]	0.36
2.	16[3-33]	13[4-39]	15[3-39]	
RLAS*				
1.	2[1-3]	2[2-2]	2[1-3]	0.97
2.	3[2-6]	3[2-6]	3[2-6]	

GOSE*				
1.	2[2-2]	2[2-2]	2[2-2]	0.80
2.	3[2-3]	3[1-4]	3[1-4]	

Table 6.4. Change in primary outcome measures in the intervention and control groups

*CRSR- Coma Recovery Scale Revised
*WHIM-MAX –Wessex Head Injury Matrix Maximum score
*WHIM-TOTAL –Wessex Head Injury Matrix Total Score
*RLAS- Ranchos Los Amigos Scale
*GOSE- Glasgow Outcome Scale Extended

a. Coma Recovery Scale Revised

The median CRSR score changed from an initial value of 5 (Range: 2-9) to a final score of 9 (Range: 4-15) in the control group while in the experimental group, this value changed from 6 (Range:2-9) to 11 (Range:5-23). There was improvement in the CRSR score post intervention in both the groups, without any statistical difference between the groups. The improvement in experimental group was better by one score.

b. Maximum WHIM Score

There was improvement in the maximum WHIM score achieved in both the groups post intervention. The median value of the maximum WHIM score changed from an initial value of 4 (Range: 3-26) to a final score of 26 (Range: 3 -57) in the control group while in the experimental group, this value changed from 3 (Range: 3 - 21) to 16 (Range: 7 - 53). No statistically significant

difference was noted between the groups in terms of improvement in the WHIM score maximum.

c. WHIM Total Score

The median WHIM Total score changed from an initial value of 4 (Range: 3-14) to a final score of 16 (Range: 3-33) in the control group while in the experimental group, this value changed from 3 (Range: 2-12) to 13 (Range: 4-39). There was improvement in the WHIM total score post intervention in both the groups, without any statistical difference between the groups.

d.RLA Score

There was improvement in the median RLA score achieved by one level in both the groups post intervention. The median value of this score changed from an initial value of 2 (Range: 1-3) to a final score of 3 (Range: 2-6)in the control group while in the experimental group, this value changed from 2 (Range: 2-2) to 3 (Range: 2-6) .No statistically significant difference was noted between the groups in terms of improvement in the RLA score.

e. Glasgow Outcome Scale Extended

The median GOSE score changed from an initial value of 2 (Range: 2-2) to a final score of 3 (Range: 2-3)in the control group while in the experimental group, this value changed from 2(Range: 2-2) to 3 (Range: 1-4). There was improvement in the GOSE score post intervention in both the groups, without any statistical difference between the groups.

6.2.1.2.Change in the subscales of CRSR

Auditory				
1.	1[0-2]	1[0-2]	1[0-2]	0.73
2.	2[1-4]]	2[0-4]	2[0-4]	
Visual				
1.	1[0-2]	1[0-3]	1[0-3]	0.52
2.	2[0-3]	2[1-5]	2[0-5]	
Motor				
1.	1[0-2]	1[0-3]	1[0-3]	0.9
2.	2[0-4]	2[0-6]	2[0-6]	
Oromotor				
1.	1[0-2]	1[0-1]	1[0-2]	0.48
2.	1[1-2]	1[0-4]	1[0-4]	
Communication				
1.	0[0-1]	0[0-1]	0[0-1]	0.36
2.	1[0-1]	1[0-2]	1[0-2]	
Arousal				
1.	2[1-2]	2[1-2]	2[1-2]	0.17
2.	2[1-3]	3[2-3]	2[1-3]	

Table 6.5. *Change in the subscales of CRSR in the intervention and control groups*

The changes in the subscales in CRSR in the control and intervention groups is shown in Table 6.5.There was no significant difference between both the groups with regard to the improvement seen in all the scales.

6.2.1.3Subgroup analysis of patients with positive SSEP

OUTCOME	CONTROL Median difference(Range)	RMNS Median difference(Range)	P Value
CRSR	**4(1,7)**	**12(9,14)**	**0.02***
WHIM Max	4(0,30)	24(13,50)	0.14
WHIM Total	3(0,24)	22(10,28)	0.14

Table 6.6 *Subgroup analysis of patients with positive SSEP*

Subgroup analysis of patients with positive SSEP median showed statistically significant difference between the two groups in the improvement in CRSR score (p=0.02). Improvement in the WHIM Max and WHIM Total scores was also better in the RMNS group, though not statistically significant.

From this we can infer that for patients with disorder of consciousness in whom the SSEP median wave is obtained, when given RMNS, the improvement in consciousness is more than that in patients who received standard coma stimulation therapy alone.

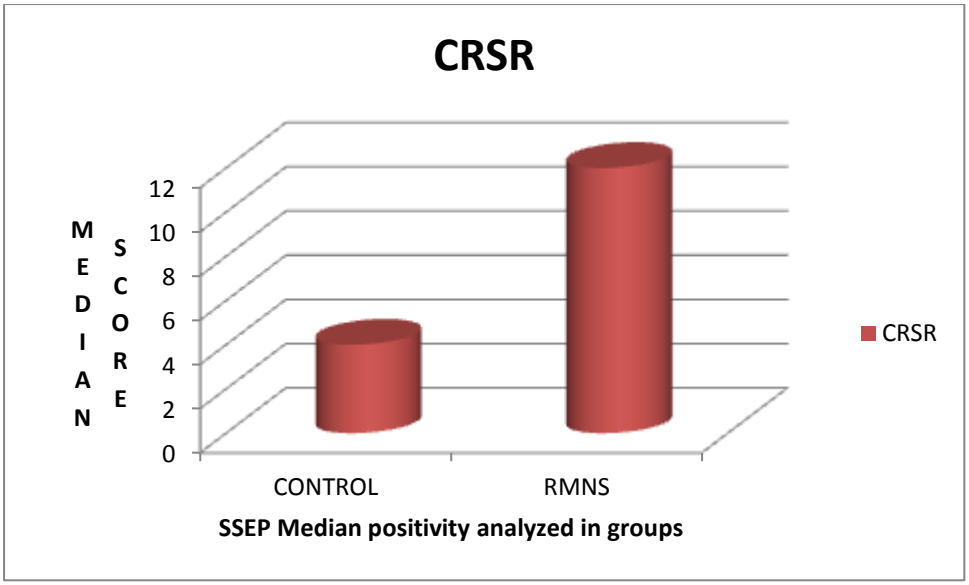


Figure 6.9 . Improvement of median score in control and RMNS group in patients with positive SSEP

6.2.1.4. Subgroup analysis of patients with duration of injury less than six months

OUTCOME	CONTROL Median difference(Range)	RMNS Median difference(Range)	P Value
CRSR	4(1,7)	9(0,14)	0.14
WHIM Max	14(0,31)	13(0,50)	0.66
WHIM Total	5(0,27)	10(2,28)	0.24

Table 6.7 *Subgroup analysis of patients with duration of injury less than six months*

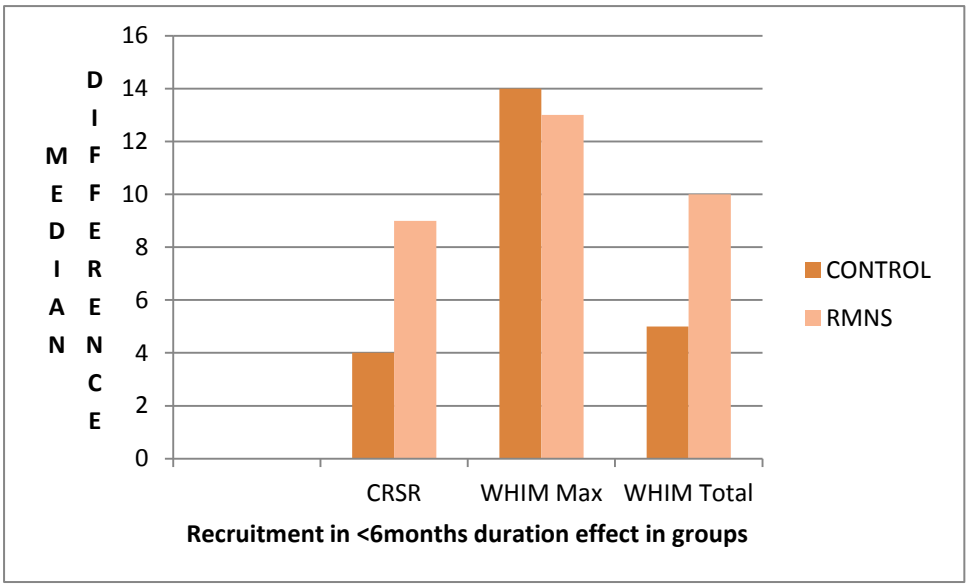


Figure.6.10 Improvement of median score in control and RMNS group in patients recruited within 6 months

Early initiation of RMNS therapy in patients were analyzed and observed that when patients are recruited for RMNS in <6months duration of injury they show more recovery as per the outcome scores, compared to those patients in control group, even though this was not statistically significant.

6.2.1.5. Comparison of maximum scores attained in the control group and intervention group in the various outcome measures

None of the measures showed any significant difference in the change in outcome between the control and intervention groups. However, comparison of maximum scores attained showed higher values in CRSR, Subscales- (Visual, Motor, Oromotor, Communication), WHIM Total and GOSE scores in the RMNS group.

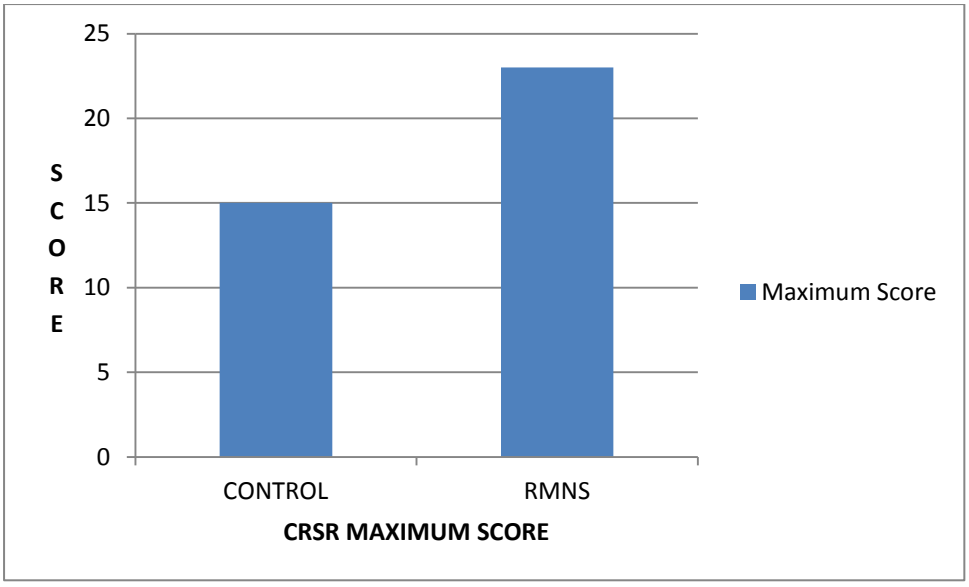


Figure. 6.11. Comparison of maximum CRSR score attained in both groups

RMNS group shows higher 'Maximum score attained' and the score attained was 23 which is the highest score in the scale, while in the control group, the maximum CRSR score attained was 15.

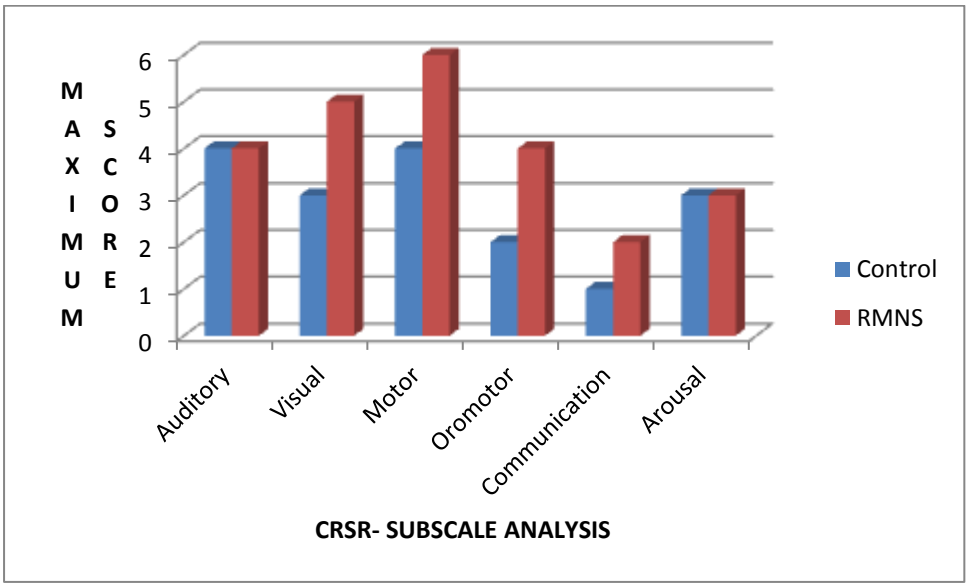


Figure 6.12. Maximum score attained for each subscale in CRSR in both the groups.

Analysis of the subscales showed that the maximum score attained in the Visual, Motor, Oromotor and Communication scales were higher in RMNS group in comparison with the control group. There was no difference in the maximum scores attained in the Auditory and Arousal sub scales.

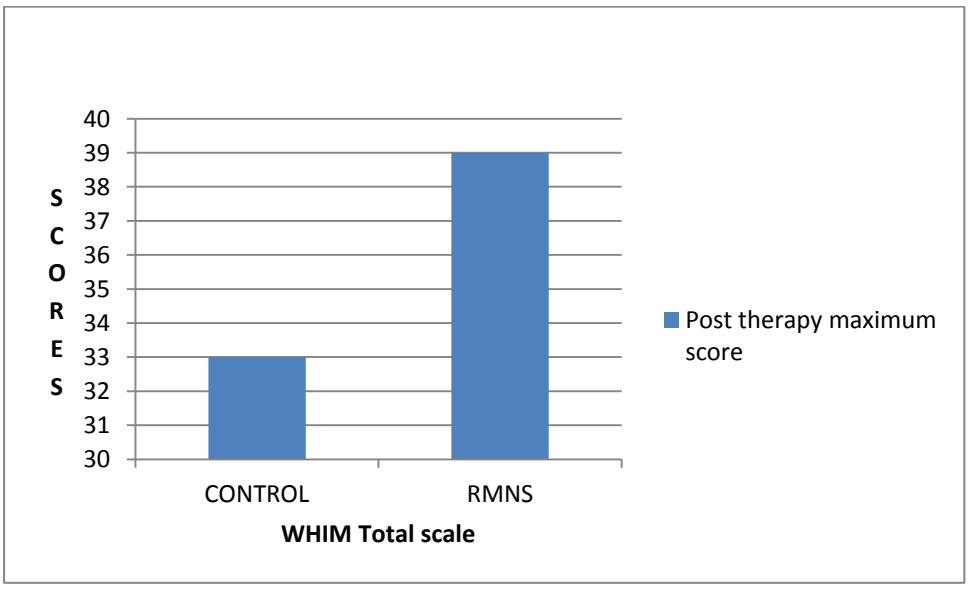


Figure 6.13. Post therapy-maximum score attained in the WHIM Total in both groups.

WHIM Score analysis showed that the highest score attained in the WHIM Total scale for RMNS group is 39 and that in control group is 33. However, in the WHIM Max Scale , the highest score attained is 57 in the control group and 53 in the RMNS group.

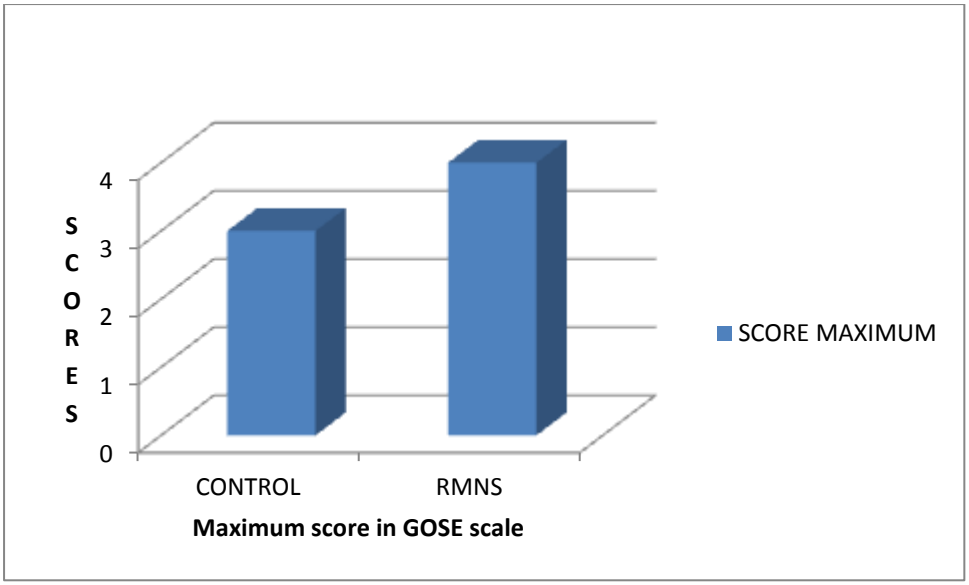


Figure 6.14. Maximum score attained in the Glasgow Outcome scale Extended (GOSE) in both groups.

In GOSE Scale analysis, 3 (Lower severe disability i.e. Needs full assistance in ADL throughout the day)was the highest level attained in the control group and 4(Upper severe disability i.e. Needs some supervision/assistance in ADL, but can be alone for >8 h/day) was the highest level attained in the RMNS group.

In RLAS Score analysis there was no difference in the maximum score attained in both the groups.

6.2.1.6. Comparison of range and median values of improvement in the various outcome scores in the two groups

P50- Median

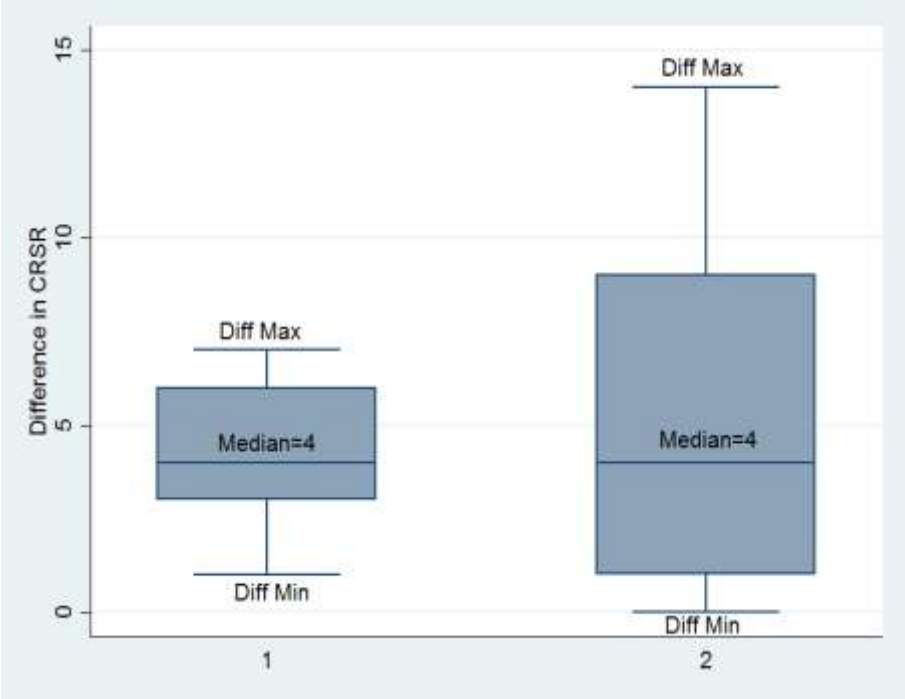
MIN- Minimum difference

MAX- Maximum difference

a. CRSR

GROUPS	P50	MIN	MAX
Control	4	1	7
RMNS	4	0	14

Table 6. 8 *Comparison of range and median value of improvement in the CRSR score in both groups*



1- Control group

2- RMNS group

Figure 6.15. Median difference in individual CRSR score with range

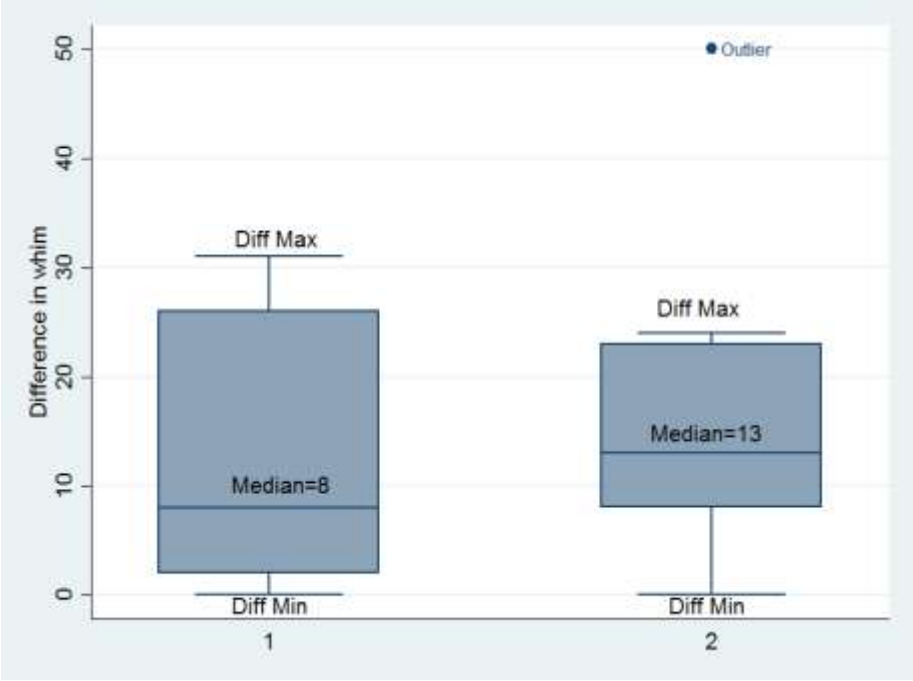
From the table and graph it is inferred that in the control group minimum difference was 1 and maximum difference was 7 with a median value of 4. In the RMNS group the minimum difference was 0 and maximum difference was 14 and its median was 4. Thus even though the median value for the difference in both the groups was same, the maximum difference attained in the RMNS

group was more than in the control group (14 and 7), even though this was not statistically significant.

b.WHIM MAX

GROUPS	P50	MIN	MAX
Control	8	0	31
RMNS	13	0	50

Table 6.9. *Comparison of range and median value of improvement in the WHIM Max score in both groups*



1- Control group
2- RMNS group

Figure. 6.16. Median difference in individual WHIM Max score with range

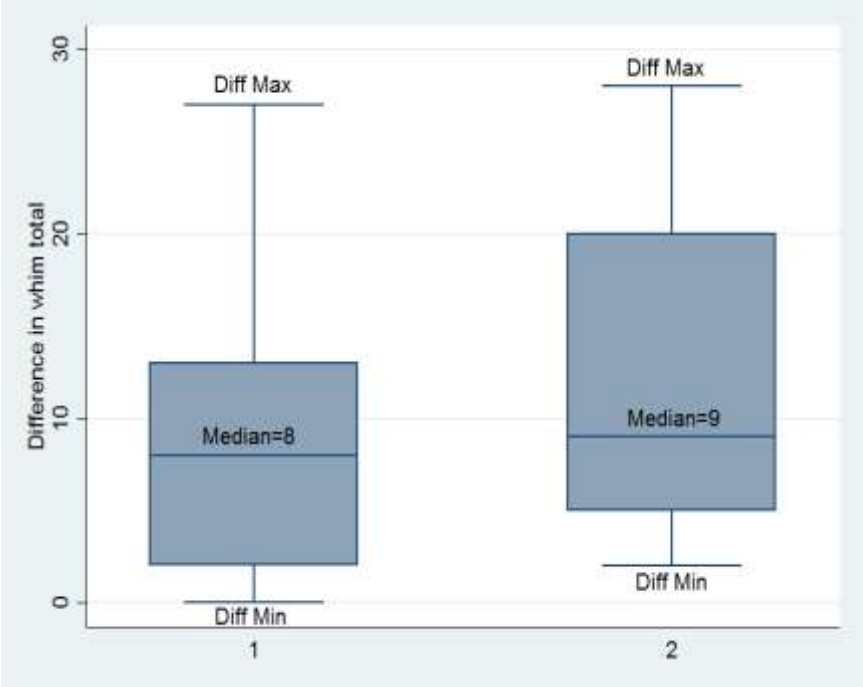
From the table and graph it is inferred that in the control group minimum difference was 0 and maximum difference was 31 with a median value of 8. In the RMNS group the minimum difference was 0 and maximum difference was 50 with a median value of 13. Thus the maximum difference attained in RMNS

group was more than control(50 and 31) even though this was not statistically significant.

c.WHIM TOTAL

GROUPS	P50	MIN	MAX
Control	8	0	27
RMNS	13	0	50

Table 6.10. *Comparison of range and median value of improvement in the WHIM Total score in both groups*



1- Control group, 2 - RMNS group

Figure. 6.17. Median difference in individual WHIM Total score with range

From the table and graph it is inferred that in the control group the minimum difference was 0 and the maximum difference was 27 with a median value of 8. However in the RMNS group the minimum difference was 0 and the maximum difference was 50 with a median value of 13. Thus the maximum difference

attained in the RMNS group was more than in the control(50 and 27) even though this was not statistically significant.

d.RLAS

GROUPS	P50	MIN	MAX
Control	1	0	3
RMNS	1	0	4

Table 6.11. *Comparison of range and median value of improvement in the RLA score in both groups*

In the control group, minimum difference was 0 and maximum difference was 3 with a median value of 1.In the RMNS group minimum difference was 0 and maximum difference was 4 and the median value was 1. Thus even though the median value for the difference in both the groups is the same , the maximum difference attained in the RMNS group was more than in the control group (4 and 3) even though this was not statistically significant.

e.GOSE

GROUPS	P50	MIN	MAX
Control	1	0	1
RMNS	1	0	2

Table 6.12. *Comparison of range and median value of improvement in the GOSE score in both groups*

In the control group the minimum difference was 0 and maximum difference was 1with a median value of 1. In the RMNS group the minimum difference was 0 and maximum difference was 2 with a median value of 1. Thus even though the median value for the difference in both the groups is the same the

maximum difference attained in RMNS group was more than control(2 and 1) even though this was not statistically significant.

6.2.2Secondary outcome measure- EEG

Post-EEG	CONTROL(N*)	RMNS(N)	P-value
Positive	2	2	0.91
Negative	8	7	

Table 6.13. *Distribution of patients in each group, in the post therapy EEG analysis.*

*N- Number

EEG- Electroencephalogram

All the pre EEG analysis showed slow wave dysfunction which is considered as negative '-' in this study. In the post EEG analysis, 20% of patients in group 1 and 22% of patients in group 2 showed alpha wave activity which is considered as positive '+' in this study.

6.3.Correlation of each variable with different outcome measures.

6.3.1. Correlation of demographic, clinical and neurophysiological variables with CRSR

Variables CRSR

	M%	P value
Age		
<30	87.5	0.86

30-50	58.6	
>50	128.6	
Gender		
Male	81.3	
Female	56.3	0.46
Duration of injury		
<6 months	120	
6 Months - 1 Yr	28.6	
>1Yr	45.2	0.16
Brain injury		
Traumatic	75	
Nontraumatic	127.8	
Combined	0	0.2
DAI		
Absent	57.1	
Present	133.3	**0.02***
Seizure		
Absent	73.8	
Present	66.1	0.93
Initial level of consciousness		
VS	58.6	
MCS	81.3	0.64
Surgery		
Not done	57.1	0.2

Done	128.6	
SSEP		
Not Obtained	57.1	
Obtained	124.3	0.28
P14 wave	0	
Not Obtained	57.1	
Obtained	103.8	0.46
VEP	0	
Not Obtained	55.6	
Obtained	108	0.16
BERA	0	
Not Obtained	57.1	
Obtained	87.5	0.43
Drugs	0	
Not Given	150	
Given	57.1	0.12

Table 6.14. *Effect of variables on CRSR*

M%= Percentage increase in the median value of CRSR score difference (ie difference in pre and post therapy CRSR values)

* Significant Pvalue

In the analysis of relation of variables to the outcome measures, Diffuse Axonal Injury showed statistically significant effect on CRSR.(P value-0.02). The median percentage increase in CRSR score for patients with diffuse axonal injury was 133% and for those patients without diffuse axonal injury it was 57%.

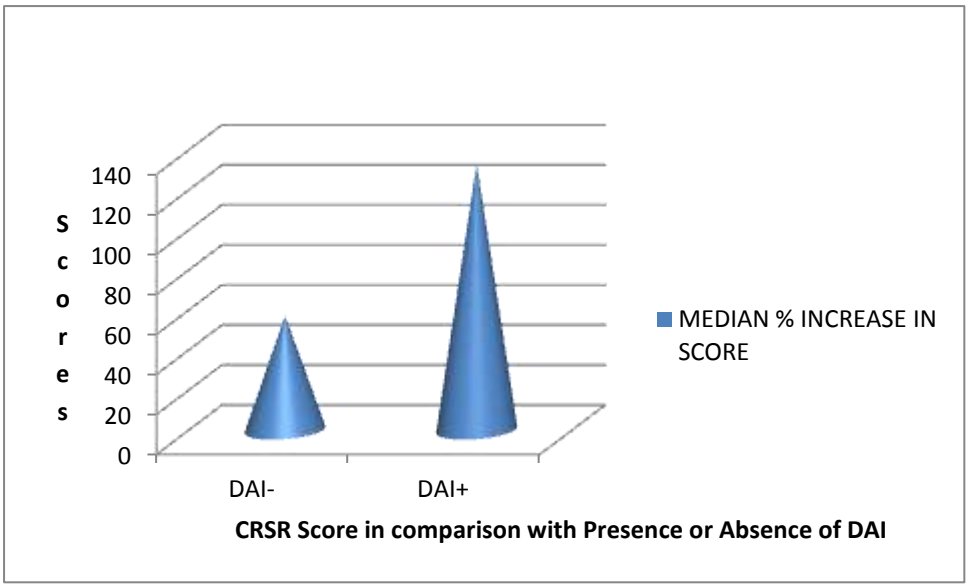


Figure 6.18. Median percentage increase in CRSR scores for patients with and without diffuse axonal injury.

Statistical analysis for the median percentage increase in CRSR scores showed that patients with age>50 years had maximum recovery followed by those in the age group of less than 30 years. Males had better recovery compared to the female patients.(81% and 56% increase respectively). Recruiting the patients earlier to the study showed more scores i.e. when the duration of injury was less than 6 months there was 120% increase in the median percentage CRSR score value. Patients with non traumatic brain injury (127% increase) showed more recovery compared to patients with traumatic brain injury. Patients without any seizure history showed better improvement in CRSR score compared to patients with history of seizures.

Those patients recruited in minimally conscious state showed better improvement than those who were recruited in a vegetative state (81% increase for MCS and 58% increase for VS)

Patient who were recruited with features of abnormal posturing (decerebration/decortications) showed less percentage increase (53%)in

recovery compared to those enrolled without features of abnormal posturing(75%).

CRSR Scores when analyzed on the basis of neuro electrophysiological study, showed that those patients who showed normal wave pattern in P14, SSEP, VEP and BERA studies have scored higher median percentage increase in CRSR score values.

Statistical analysis also showed that neuro stimulatory medications have not brought any significant effect in the median percentage increment for CRSR score value.

6.3.2 Correlation of demographic, clinical and neurophysiological variables with the subscales of CRSR

Variables	M^A	M^V	M^M	M^O	M^C	M^Ar
Age						
<30	1	1	1	1	0	0
30-50	1	1	0.5	0	0	1
>50	1	2	0	1	1	0
Gender						
Males	1	1	0.5	1	0	0
Females	1	1	0.5	0.5	0	1
Duration of injury				*		
<6 months	1	1	1	1	0	0
6 Months - 1 Yr	1	1	0	0	0	0
>1Yr	1	1	0	0	0	1

Mode of injury						
Traumatic	1	1	1	1	0	1
Nontraumatic	1.5	0.5	0.5	1	0	0.5
Combined	0	0	0	0	0	0
DAI	*		*	*		
Absent	1	1	0	0	0	0
Present	2	2	1	1	1	1
Seizure						
Absent	1	1	0	1	0	1
Present	0.5	1	1	0.5	0	0
Initial consciousness status					*	
VS	1	1	0	0	0	0
MCS	2	2	1.5	1	1	1
Abnormal posture					*	*
Present	1	1	0	0	0	1
Absent	1	2	1	1	1	1
Surgery					*	
Not done	0.5	1	0.5	0	0	0
Done	1	2	1	1	1	1
SSEP	*	*	*		*	
Not Obtained	1	1	0	0	0	0
Obtained	1.5	2	1	1	1	1
P14 wave						
Not Obtained	0	1	1	0	0	0

Obtained	1	1.5	0	0.5	0	1
VEP						
Not Obtained	1	1	0	0	0	1
Obtained	1	1	0.5	1	0	0
BERA						
Not Obtained	0	1	1	0	0	1
Obtained	1	1	0	1	0	0
Drugs						
Not Given	1	2	1	1	0	0
Given	1	1	0	0	0	1

Table 6.15.*Effect of variables on CRSR Subscales*

M^= Median difference

A= Auditory

V=Visual

M=Motor

O=Oromotor

C=Communication

Ar=Arousal

* statistically significant (p-value <.05)

Statistical Analysis for the subscales showed the following results. In auditory subscale analysis SSEP positivity and presence of diffuse axonal injury showed statistically significant effect on the auditory responses. (p-value-.03 and p-value.04 respectively).

In the visual subscale analysis, SSEP positivity showed statistically significant effect on the visual scores (p value =.05).

In the motor subscale analysis, initial consciousness status i.e. patients in minimally conscious state showed statistically significant difference in the motor response compared to those in vegetative state at the time of initiation of the therapy.(p-value=.01).

In the oromotor subscale analysis, duration of injury and diffuse axonal injury have statistical significant effect on these scores (p-value=.03, p-value=.03 respectively).

Communication subscale analysis showed that initial consciousness status , history, of surgical decompression, SSEP positivity and presence of normal posture have statistical significant effect on the scores (p-value=.02, p-value=.04, p-value=.001 and p-value-.02 respectively).

In the arousal subscale, absence of decorticate and decerebrate rigidity had statistical significant effect on these scores (p-value=.07).

Thus patients in whom SSEP median results were positive improved better in almost all the subscales of CRSR when compared to patients with absent SSEP median.

6.3.3.Correlation of demographic, clinical and neurophysiological variables withWHIM scores

Variables	WHIM max		WHIM total	
	M%	p-value	M%	P-value
Age				
<30	233.33		166.67	
30-50	69.05		83.33	

>50	433.33		333.33	
Gender				
Males	216.67		216.67	
Females	187.50		144.6	
Duration of injury				
<6 months	225.00		254.55	
6 Months - 1 Yr	29.17		66.67	
>1Yr	169.05		120.83	
Mode of injury				
Traumatic	200.00		166.67	
Nontraumatic	216.67		212.50	
Combined	233.33		350.00	
DAI				
Absent	225.00		114.29	
Present	200.00		254.55	
Seizure				
Absent	229.17		214.77	
Present	112.00		66.67	
Initial consciousness status				
VS	229.17		107.14	
MCS	175.00		295.83	
Abnormal Posture				
Present	50.00	*0.01	66.67	*0.04

Absent	300.00		300.00	
Surgery				
Not done	229.17		144.64	
Done	200.00		254.55	
SSEP				
Not Obtained	225.00		100.00	
Obtained	175.00		260.61	
P14 wave				
Not obtained	233.33		166.67	
Obtained	14.58		83.33	
VEP				
Not Obtained	233.33		175.00	
Obtained	245.83		140.48	
BERA				
Not Obtained	33.33		66.67	
Obtained	266.67	*0.04	266.67	*0.008
Drugs				
Not Given	233.33		300.00	
Given	200.00		114.29	

Table 6.16. *Effect of variables on WHIM Scores*

M%= Percentage increase in the median value of WHIM score difference (ie difference in pre and post therapy WHIM values)

Pv= P value

*= Statistically significant P value

Presence of abnormal posture has shown statistically significant influence on maximum and total scores of WHIM scales. (WHIM max: p-value=0.01, WHIM total: p-value=.04). Analysis showed higher increase in median percentage score when a patient has no abnormal posturing (like decorticate or decerebrate posturing) at the time of recruitment.

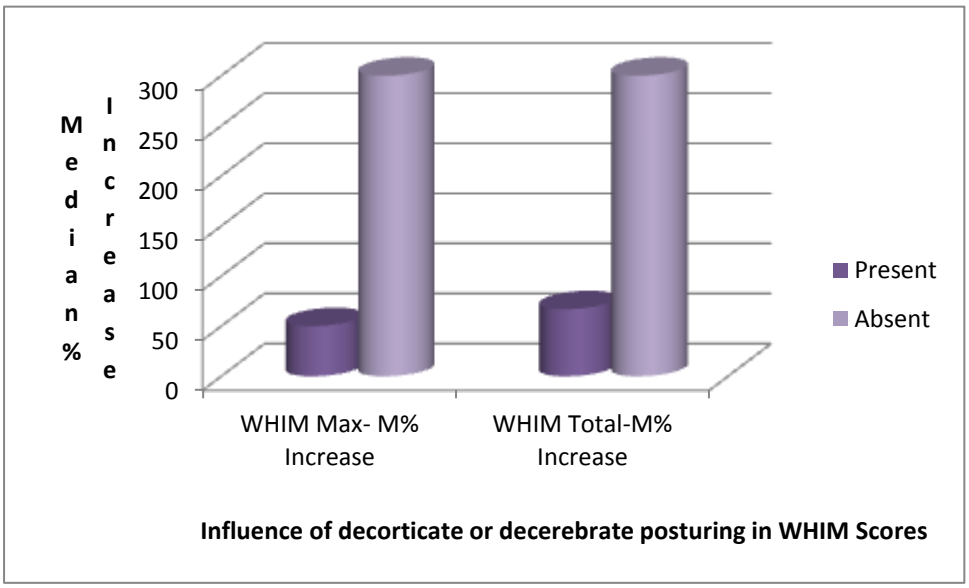


Figure 6.19. WHIM score variations with respect to abnormal posture.

Brain stem evoked auditory response(BERA) positivity has shown statistically significant effect on maximum and total scores of the WHIM scale.(WHIM max: p-value=.04, WHIM total: p-value=.008)

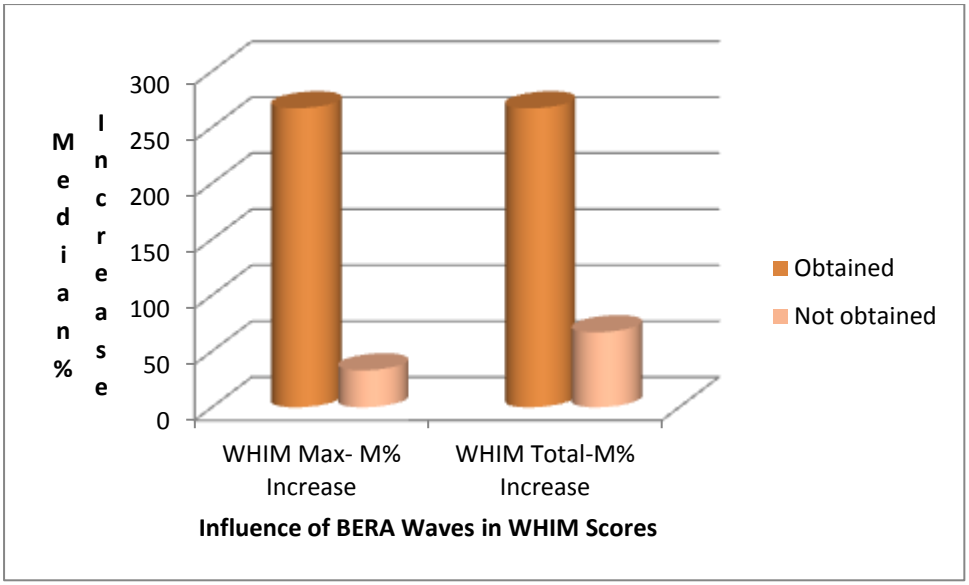


Figure 6.20. WHIM score variations with respect to BERA

Median percentage increase in WHIM max scoring corresponding to each variable was almost similar to that seen in CRSR Score analysis except that corresponding to diffuse axonal injury(absence of DAI caused 25% more increase in WHIM max score compared to presence of DAI). However, this was not statistically significant.

6.3.4Correlation of demographic, clinical and neurophysiological variables with RLA and GOSE scores

Variables	RLAS		GOSE	
	M%	p-value	M%	p-value
Age				
<30	50.00		50.00	
30-50	25.00		0.00	

>50	50.00		50.00	
Sex				
Males	50.00		50.00	
Females	25.00		25.00	
Duration of injury				
<6 months	50.00		0.00	
6 Months - 1 Yr	50.00		50.00	
>1Yr	50.00		50.00	
Mode of injury				
Traumatic	50.00		50.00	
Nontraumatic	25.00		25.00	
Combined	50.00		50.00	
DAI				
Absent	50.00		50.00	
Present	50.00		25.00	
Seizure				
Absent	50.00		50.00	
Present	58.33		25.00	

Initial consciousness status				
VS	50.00		0.00	
MCS	83.33	*0.006	50.00	*0.02
Abnormal Posture				
Present	25.00		25.00	
Absent	50.00		50.00	
Surgery				
Not done	50.00		50.00	
Done	50.00		50.00	
SSEP				
Not Obtained	50.00		0.00	
Obtained	50.00		50.00	
P14 wave				
Not Obtained	0.00		0.00	
Obtained	25.00		25.00	
VEP				
Not Obtained	50.00		50.00	
Obtained	50.00		25.00	

BERA				
Not Obtained	0.00		0.00	
Obtained	50.00		50.00	
Drugs				
Not Given	50.00		25.00	
Given	50.00		50.00	

Table 6.17. *Effect of variables on RLA and GOSE Scores*

M%= Percentage increase in the median value of RLAS and GOSE score difference (i.e. difference in pre and post therapy RLAS/ GOSE values)

P = P value

*= Statistically significant P value

Initial consciousness status showed statistically significant influence on the RLAS and GOSE outcome scores(p-value for RLAS= 0.006 and p-value for GOSE=0.02)

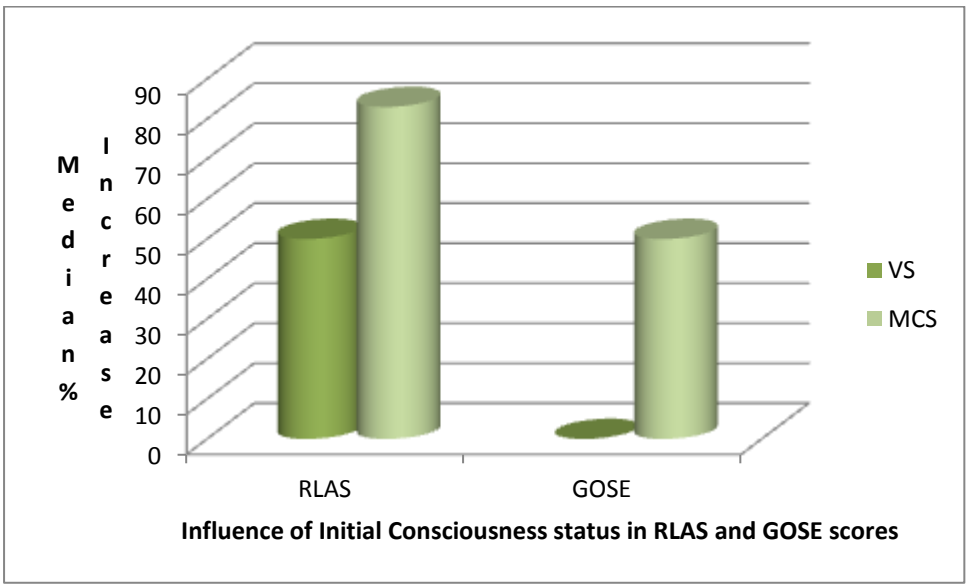


Figure 6.21. Median percentage increase in RLA/GOSE outcome scores analyzed with respect to initial consciousness status.

Median percentage increase in RLA and GOSE scoring corresponding to all the other variables were almost similar to that seen with CRSR Score analysis except that diffuse axonal injury did not show a statistically significant effect on these scores. Similarly duration of injury at the time of recruitment (early recruitment), history of decompression surgery, absence of seizures , presence of VEP and SSEP waves and administration of neurostimulatory drugs could not show any significant positive influence on median percentage increase in RLAS/GOSE scores.

In the control group 7 out of 13 patients (53%) in vegetative state improved to minimally conscious state and in the RMNS group 8 out of 11 patients (72%) in vegetative state improved to minimally conscious state. But this improvement in RMNS group was not statistically significant.

6.4 Multivariate analysis for variables which showed statistically significant effects on scores.

6.4.1. Multivariate analysis from linear regression (CRSR score)

Variables	Regression coefficient[a]	95% CI	p-value
DAI			
Absent	Ref*		0.018
Present	4.5	0.9, 8.1	
Group			0.448
1	Ref		

2	1.1	-1.9, 4.2	

Table 6.18.*Multivariate analysis from linear regression*

[a] = coefficient for the difference between pre and post CRSR score

* Reference

Comparing to patients in whom there was no diffuse axonal injury, patients with diffuse axonal injury have 4.5 units increase in the difference of CRSR score when adjusted for group and it is statistically significant with p-value of 0.018. However there is no significant (p=0.448) difference between the control and intervention groups in the CRSR score in both the bivariate and multivariate analyses.

6.4.2 Multivariate analysis from linear regression (WHIM Max)

Variables	Regression coefficient[a]	95% CI	p-value
Abnormal Posture			0.138
Absent	10.2	-3.9, 24.2	
Present	Ref		
BERA			0.825
Obtained	1.5	-13.6,	

		16.7	
Not obtained	Ref		
Group			
1	Ref		0.924
2	-0.5	-7.2, 22.5	

Table 6.19 *Multivariate analysis from linear regression (WHIM Max)*

[a] coefficient for the difference between pre and post Whim max score

* Reference

Comparing to patients in whom BERA was absent, patients in whom BERA was present had 1.5 units increase in the difference of WHIM Max score. Similarly, comparing to patients with abnormal posture, patients with normal posture had 10.2 units increase in the difference of WHIM Max score, when adjusted for group. But these results were not statistically significant. So also, there was no statistically significant (p=0.924) association between the intervention and control groups is both the bivariate and multivariate analysis.

6.4.3.Multivariate analysis from linear regression (WHIM Total)

Variables	Regression coefficient[a]	95% CI	p-value
Abnormal Posture			0.043
Absent	8.8	0.3, 17.3	
Present	Ref		
BERA			0.590

Obtained	2.3	-6.9, 11.4	
Not obtained	Ref		
Group			0.727
1	Ref		
2	-1.2	-8.5, 6.2	

Table 6.20. *Multivariate analysis from linear regression (WHIM Total)*

[a] - coefficient for the difference between pre and post WHIM total score

Ref- Reference

Comparing to patients in whom BERA was absent, those in whom BERA was present had 2.3 units increase in the difference of WHIM Total score. But this was not statistically significant. Comparing to patients with abnormal posture, patients with normal posture have 8.8 units increase in the difference of WHIM Total score, when adjusted for group and this was found to be statistically significant with a p-value of 0.04. However, there was no significant (p=0.727) difference between the groups in both the bivariate and multivariate analysis.

7. DISCUSSION

The aim of the study was to study the effectiveness of electrical stimulation of the right median nerve to improve arousal in patients in vegetative and minimally conscious states within one and half years after acquired brain injury.

70% of the patients recruited had duration of injury less than 6 months. Mean duration of injury was 21.35 weeks and range was 4-59 weeks.
Majority (80%) of the patients had impaired consciousness secondary to traumatic brain injury where as in the remaining , the aetiology was Nontraumatic. One patient who was in control group had combined injury.(cardiac arrest and hypoxic damage after sustaining trauma). This was similar to the fact described in the previous studies that the most common cause of acquired brain injury is trauma.(5)
Presence of epileptiform disorder has adverse effect on disorders of consciousness, as both these diseases converge on a common set of cortical and sub cortical structures. Therefore, history of seizures was taken at the time of enrolment.(59)
Both vegetative (85%) and minimally conscious state (15%) patients were recruited for the study . Similar results were noted in the previous studies evaluating the efficacy of median nerve stimulation. (3)(57)
42% of patients had abnormal posturing (decerebration /decortication) at the time of recruitment. Previous studies state that presence of decorticate /decerebrate posturing may be a predictor of prolonged vegetative state(60).
Diffuse axonal injury was present on imaging in 23% of the patients.
52% had surgical management with decompression craniectomy while the others were managed conservatively. This history was also taken to check whether it becomes a confounding factor. History of decompressive craniectomy might give a clue regarding the severity of injury and the possible

complications including cerebral scarring, cortical vein rupture, infections etc. that would have occurred.(61)(62)

60% patients received cognitive stimulants including Modafinil, Syndopa, Amantadine, Zolpidem etc. in addition to the coma stimulation programme during their rehabilitation.

SSEP Median study, BERA and VEP were positive in 38%, 75% and 76% of the patients respectively in whom the study was done.EEG showed slow wave dysfunction in all the patients. Electrophysiological analysis mainly evoked potential studies were done to check the brain activity status, at the time of recruitment. SSEP Tibial was absent for all the patients for whom the study was done. This may be implying the fact that upper limb stimulation is better in coma arousal programmes compared to stimulation in lower limb. Further studies are needed to prove or disprove this.

Outcome measures used in this study were CRSR, WHIM, RLAS AND GOSE. In the 2003,2005 studies by Cooper et al, GCS was used as the outcome measure.(57) (3) In the study which was conducted at Bangalore Baptist Hospital ,the outcome measures used were Western Neurosensory stimulation profile and GCS.(58) In Coopers study, the patients were mainly recruited from the Neurology intensive care unit where as in our study patients were recruited from the rehabilitation wards and hence were more medically stable.

There was no significant difference between the two groups in improvement of any of the outcome measures. There was no significant difference between both the groups with regard to the improvement seen in all the subscales of CRSR as well.

Though there was no statistically significant differences between the two groups with regard to these variables, the experimental group had more number of patients in vegetative state and diffuse axonal injury, more patients with duration of injury more than 6 months and more number of patients with

abnormal posturing. This could have contributed to the non significant outcomes seen with the median nerve stimulation.

On analysis of a subgroup of patients with SSEP median positive results, patients in the experimental group had significantly more improvement in CRSR score than in control group. (p value <0.02). This is an important result and indicates that only patients with positive SSEP median results may benefit from RMNS. Similarly patients with duration of injury less than six months showed better results in the experimental group than in the control group.

Comparison of maximum scores attained could show higher values of CRSR, Subscales- (Visual, Motor, Oro motor, Communication), WHIM Total and GOSE values in the experimental group. This was similar to the outcome findings seen in two studies quoted earlier.(58) In those studies, results showed increased score for the consciousness status of the patients , though not statistically significant.

Here, in this study, one patient in the RMNS group showed higher 'Maximum score attained' and the score attained was 23 which is the highest score in the CRSR scale. This patient was a female who had traumatic brain injury with diffuse axonal injury, and presented in a minimally conscious state. She was recruited for the study during the 7^{th} week of injury. She showed remarkable improvement with coma stimulation along with RMNS assessed by CRSR and WHIM scorings. Her pre EEG analysis showed slow wave dysfunction with majority of theta and delta waves and post therapy EEG showed waves suggestive of wakefulness viz. Alpha and beta waves.(24) Her pre therapy CRSR score was 9, WHIM Max score was 16, WHIM Total score was 11, RLA score was 2, and GOSE score was 2, which became 23, 40, 39,6 and 4 in the post therapy assessment respectively.

Similarly, the highest score attained in the WHIM Total scale in the RMNS group was 39 and that in control group was 33. This difference was not statistically significant. Since WHIM assesses the neuro behavioural function in

detail with a maximum score value of 62, within the short span of 4weeks it is difficult to expect a dramatic hike in the score value.
No other studies have used GOSE and RLAS for coma stimulation outcome assessment as these scales are not sensitive enough to pick up the improvements that occur in these patients.

Statistical analysis for the median percentage increase in CRSR scores showed that patients in the age group of >50yrs showed maximum recovery. This was in contradiction to the previous studies which points to a better chance of recovery in younger age group.(63) The next age group which showed better recovery were patients in the age group of <30 years who showed a recovery more than the middle aged patients. This was in conjunction with the previous literature.

In the analysis males showed more recovery compared to the female patients. (81% and 56% increase respectively). This was similar to the observations in previous studies.(64)
Non traumatic brain injury patients compared to traumatic brain injury patients showed more recovery (127% increase in the median CRSR score). This was not in line with the previous studies were patients with traumatic causes of brain injury showed better chance of recovery than non traumatic causes like hypoxic ischemic sequalae.(65)
Recruiting the patients earlier to the study showed more scores i.e. when the duration of injury was less than 6 months, there was 120% increase in the median CRSR score . Subgroup analysis did not show any significant difference between the groups. These patients showed statistically significant improvement in the oromotor subscale of CRSR in both groups.
The nonsignificant results on the outcome measures could have been due to the severity of brain injury and due to the fact that 23% of patients had duration of injury more than 6 months while most of the previous studies enrolled patients during the acute period within one month of injury. Moreover, the stimulation

was given for only two sessions each of one hour duration every day for 40 sessions while in most of the previous studies, the stimulation was given for about 8 hours per day for 3 months .This point was highlighted in the previous studies as earlier the initiation of coma stimulation, higher is the chance of response to therapy and faster will be the recovery.(64)(66) Patients without any seizure history showed better improvement in CRSR score compared to patients with history of seizures. Presence of seizure, fever etc. may affect the prognosis adversely.(59)(67)

Those patients who were recruited in minimally conscious state showed better improvement than those who were recruited in a vegetative state (81% increase in the CRSR median score value for MCS and 58% increase for VS)(68)(6) Statistical analysis showed that patients in minimally conscious state showed a statistically significant improvement in the communication subscale of CRSR as well as with the GOSE($p=0.02$) and RLA scores ($p=0.006$)as compared to the patients in vegetative state in both the groups.

Progress in therapy was separately analysed to check if abnormal posturing had any influence on outcome measures.(69) Patients with features of abnormal posturing (decerebration /decortications) showed less percentage increase in the median CRSR score value (53%)in recovery compared to those enrolled without features of abnormal posturing(75%).(70)(71)It was seen that patients without abnormal posturing had statistically significant improvement in the communication and arousal subscales of CRSR as well as with the WHIM max($p=0.01$) and the WHIM total($p=0.04$)scores .

Statistical analysis showed significance for the presence of diffuse axonal injury associated with the traumatic brain injury with the total CRSR score ($p=0.02$) and also the auditory, verbal, motor and oromotor subscales of CRSR . There was no statistically significant difference in the number of patients with diffuse axonal injury in both the groups.DAI is generally a negative predictor for improvement in patients with disorders of consciousness. Previous studies have

shown that presence of grade 2 and grade 3 DAI will result in persistent vegetative state.(37).But grade 1 DAI has not been seen as a reason for prolonged DOC.(66)

Statistical analysis also showed that presence of neuro stimulatory drug has not brought any significant effect in the median percentage increment for CRSR score value. Previous studies had shown improvement in consciousness status with pharmacological interventions. (31)

Patients who showed normal wave pattern in P14, SSEP, VEP and BERA studies scored higher median percentage increase in CRSR score values. This was in conjunction with the previous studies.(29)(24) Patients with positive median SSEPs had significant improvement in the arousal, verbal, motor and oromotor subscales of CRSR.

P14 wave analysis was done for 13 patients to check for spinal cord dysfunction and its influence on the prognosis of disorder of consciousness. 103% increase in the median value of CRSR score difference (i.e. difference in pre and post therapy CRSR values) was seen in those with P14 wave positivity and only 57% increase was seen in those with absent P14. (It gives an idea about the conductivity of electrical impulses through the cord) (29)(72)

Visual and auditory evoked potential analysis were done to check the effectiveness of other coma stimulation modalities adopted for routine therapy. Previous studies state that the visual and auditory pathways have synaptic connection with the ARAS centre so that the parallel auditory and visual stimulations may have an additional effect on RMNS therapy(73)(74)

All the pre intervention EEG analysis showed slow wave dysfunction .

In the post intervention EEG analysis, 20% of patients in the control group and 22% of patients in the RMNS group showed alpha wave activity.(24) Those with positive auditory evoked responses had significant improvement on the WHIM max ($p= 0.04$) and WHIM total scores ($p= 0.008$).

No other study has done statistical analysis for the CRSR subscales with the previously mentioned variables. In this study the auditory, visual, motor, oro motor, communication and arousal subscales were analyzed with the various variables.

Better auditory and visual scores in RMNS group compared to control group has been seen in previous studies. This conveys that improvement in auditory and visual responses may be possible with somatosensory stimulation(75)(76)(77). The relation of somatosensory input and auditory/Visual function gives idea about Multisensory integration. The explanation for this is seen in previous studies as somatosensory pathway has synaptic connections with auditory pathway and visual pathway (Multisensory integration). These neural circuits are in relation with ARAS which in turn synapses with BFPV neurons (basal forebrain parvalbumin neurons). The stimulation of BFPV neurons increases GBO (Gamma band oscillations) which is seen in EEG. This indicates active cortical processing/ wakefulness. The relation of auditory scores with SSEP can be related to one of the recent studies published in Pub Med.(78) ARAS has influence on auditory steady state response and Optic/Visual responses. Impaired consciousness states like vegetative state can be treated by keeping those neurons as target area of stimulation.

Presence of abnormal posture showed statistically significant influence on maximum and total scores of WHIM scale. (WHIM max: p-value=.02, WHIM total: p-value=.04). Analysis showed higher increase in median percentage score when a patient has normal posture at time of recruitment.(70)(71)Brain stem evoked auditory response(BERA) positivity also showed statistically significant effect on maximum and total scores of WHIM scales.(WHIM max: p-value=.04, WHIM total: p-value=.008)(79)(74)

As diffuse axonal injury showed a significant effect on CRSR score value in bi variate analysis, multivariate analysis was done. Comparing to patients in whom there was no diffuse axonal injury, patients with diffuse axonal injury have 4.5 units increase in the difference of CRSR score when adjusted for group and it is statistically significant with p-value of 0.018. It may be that these patients might be having only Grade 1 DAI. The grade of DAI was not recorded in this study. Further studies may be helpful to prove or disprove this. However there is no significant (p=0.448) difference between the control and intervention groups in the CRSR score in both the bivariate and multivariate analyses.

As presence of BERA and normal posture at the time of recruitment showed a significant effect on WHIM Max score value in bi variate analysis, further multivariate analysis was done, but failed to show any significant results.

As presence of BERA and normal posture at the time of recruitment showed a significant effect on WHIM Total score value in bivariate analysis these variables were taken for multivariate analysis, but again failed to show significant results.

7. CONCLUSION

1.The improvement in the level of consciousness as measured by CRSR, WHIM Total, WHIM Maximum, GOSE and RLA scores of patients in vegetative and minimally conscious states who received right median nerve electrical stimulation in addition to the standard coma stimulation programme was not significantly different from that observed in those who received only the standard coma stimulation programme (p=0.57, p=0.36, p=0.68,p=0.97, p=0.80 respectively). The improvement in the median value of CRSR post therapy was better in the intervention group by 1 score. Analysis of the CRSR subscales also did not show any statistically significant difference between the two groups.

2. Analysis of a subgroup of patients with SSEP median positivity showed better improvement in CRSR score in the RMNS group, which was statistically significant(p= 0.02). Similarly analysis of a subgroup of patients with duration of the injury less than six months showed better results in the RMNS group.

3.The highest scores attained in the CRSR,WHIM Total and GOSE scores was seen in the intervention group. The maximum score attained in the Visual, Motor, Oromotor and Communication subscales of CRSR were higher in RMNS group in comparison with the control group. There was no difference in the maximum scores attained in the Auditory and Arousal subscales.

4.The maximum value of improvement of CRSR, WHIM Total and WHIM Max scores was higher in the RMNS group than in the control group.

5.Twenty % of patients in group 1 and Twenty two % of patients in group 2 showed alpha wave activity on the EEG done post therapy which can be considered as sign of wakefulness. The result was not statistically different between the two groups.

6. In both the groups, patients with DAI had a better percentage increase in the median value of CRSR score difference compared to those without DAI and this was statistically significant($p=0.02$). Patients with absence of abnormal posturing and positive BERA results had statistically significant association with the improvement in WHIM Maximum($p=0.01$ and 0.04) and WHIM Total scores($p=0.04$ and 0.008).

7. Compared to patients in vegetative state at the time of recruitment, patients in minimally conscious state showed statistically significant improvement in the RLA($p=0.006$) and GOSE scores ($p= 0.02$). No statistically significant difference was seen between the two groups.

8. Younger age group, male gender, duration of injury less than 6 months, non traumatic brain injury, absence of seizure history, minimally conscious state, absence of decerebrate or decorticate posturing and history of decompressive surgery were other factors associated with better outcomes as measured by the CRSR score in both the groups. None of these associations were statistically significant.

9. Normal cortical wave pattern in SSEP median, VEP and BERA studies and presence of P14 wave obtained in SSEP median study are associated with better outcomes. Patients with positive median SSEPs had significant improvement in the arousal, verbal, motor and oromotor subscales of CRSR.

103% increase in the median value of CRSR score difference was seen in those with P14 wave positivity and only 57% increase was seen in those with absent P14.

10. None of the patients had any adverse effects during the procedure which was completely non invasive. More careful selection criteria for inclusion of patients and a larger sample size with more hours of stimulation over a longer duration may show significant results, so that right median nerve stimulation can be an useful adjunct in the management of patients in vegetative and minimally conscious states.

8. LIMITATIONS OF THE STUDY

1. The sample size was small. The number required for statistical significance at a CI of 95% could not be achieved in the intervention arm.
2. P14 wave form was studied only for few(13 patients) and conclusions were derived from those observations.
3. Stimulation was given only for two sessions each lasting for one hour in a day for 40 sessions. 23% of patients in the current study had duration of injury more than 6 months. Most of the previous studies tried the stimulation on patients during the acute period within one month of injury and continued for several months before a significant improvement could be seen.

9. SCOPE FOR FUTURE RESEARCH

1. A similar study with a larger sample size may show statistically significant results with CRSR and WHIM scale analysis.
2. Future studies can include only patients with SSEP median positivity.
3. Duration of study was lesser compared to that in previous studies, so studies with median nerve stimulation over a longer duration can be attempted with more hours of daily stimulation.
4. Questionnaires or outcome scores assessing the satisfaction and perception of primary caretakers can be tried as the immediate care givers are the best persons who can pick up minor changes in the consciousness and response status of patients.
5. Varying frequencies and intensities of current can be tried for stimulation to avoid adaptation to stimulation.
6. Outcome measure can include EEG analysis for GBO(Gamma Band Oscillations) by BFPV(Basal forebrain Parvalbumin) neurons and fMRI studies.
7. Further studies are needed to prove or disprove whether stimulation given to the upper limb or lower limb is better in coma arousal programmes as SSEP Median showed cortical potentials more often than SSEP Tibial.
8. Future studies can assess if patients with DAI improve better than with other injuries.

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11. ANNEXURE

1. Institutional Review Board Acceptance letter

2. Institutional Review Board Fund Grand

3. Patient Information sheet and consent form

4. JFK- Coma Recovery Scale Revised score sheet

5. Wessex Head Injury Matrix score sheet

6. Ranchos Los Amigos scale score sheet

7. Glasgow Outcome Scale Extended score sheet

Dr. Remya Mathew and Dr. Raji Thomas were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members. After discussion, it was resolved to be **ACCEPT the proposal AFTER receiving the suggested modifications and answers to the queries.**

Note:
1. Kindly HIGHLIGHT the modifications in the revised proposal.
2. Keep a covering letter and point out the answer to the queries.
3. Reply to the queries should be submitted within 3 months duration from the time of the thesis/ protocol presentation, if not the thesis/protocol have to be resubmitted to the IRB.
4. The checklist has to be sent along with the answers to queries.

Email the details to research@cmcvellore.ac.in and send a hard copy through internal dispatch to Dr. Nihal Thomas, Addl. Vice-Principal (Research), Principal's Office, CMC.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Raji Thomas, Physical Medicine and Rehabilitation, CMC

IRB Min. No 8603 dated 11.12.2013

Ethics Committee Silver, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

and the patient information / informed consent. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

The trial need to be registered with Clinical Trial Registry India (CTRI) http://ctri.nic.in before commencing.

The study will need to be submitted to a three monthly data-safety monitoring board (DSMB) review with duly filled in form found in the link http://172.16.11.136/Research/IRB_Polices.html

Fluid Grant Allocation:

A sum of 83,333 INR (Rupees Eighty Three Thousand Three Hundred and Thirty Three only) will be granted for 20 months.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Raji Thomas, Physical Medicine and Rehabilitation, CMC

Ethics Committee Silver, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INFORMATION SHEET AND INFORMED CONSENT

Christian Medical College, Vellore
Department of Physical Medicine and Rehabilitation

An interventional study in which the Right Median nerve electrical stimulation for patients with acquired brain injury who are in subnormal conscious state for increasing the wakefulness, arousal and responsiveness.

Information sheet

You are being requested to allow the patient to be participated in a study to assess the Role of peripheral nerve electrical stimulation in improving wakefulness, functional response and recovery from subnormal conscious state in patients with moderate to severe acquired brain injury. We hope to include about 32 people from this hospital in this study.

How does right median nerve electrical stimulation study help?

There are many studies previously done to find the effectiveness of this in increasing the wakefulness and response status in disordered consciousness patients. Mainly it works by stimulating the wakefulness centre in the dominant hemisphere of the brain.

Do procedures in the study have any side effects or complications?

There are no known procedure related complications.

If your patient takes part for what will he/she will be taken for?

If you agree to take your (relationship---) to participate in this study, he/she will be assigned to one of the two groups- the trial group or the control group. This will be done using computer generated random numbers, and the primary investigator or you will not know to which group the patient will be allocated to. The trial group will receive electrical stimulation to the nerve in the hand using electrodes placed on the palmar aspect of the wrist to send electrical impulses through the nerve to the brain. The control group also will have electrodes placed on the palmar aspect of the wrist, however the wires are cut and hence these patients will not receive the electric stimulation..The stimulation will be given by the occupational therapist who alone is informed which group the patient belongs to.

The standard coma stimulation programme will continue for both groups. The electrical stimulation will feel like a feeble vibration sense and that is given with Functional Electrical Stimulation device. Each therapy session last for one hour, and two such sessions per day are given. Ten sessions of therapy per week are planned for four weeks. Thus the patient will undergo 40 sessions of stimulation or sham therapy in total during the whole study. All other treatments that the patient is already on will be continued and their regular treatment will not be changed during this study. The patient will be examined and assessed with a recovery scale before and after the therapy for the comparison of the values by the investigating doctor.

The patient will be taken for an EEG test after the completion of therapy to assess the brain activity changes. No other procedures or blood tests will be conducted routinely for this study.

If at any time the bystanders note any problems, they are expected to report this to the investigating doctor. The patient will also be visited by the doctors during the study.

The doctors you can contact are:

Dr.Remya Mathew, department of PMR.

Dr.Raji Thomas, department of PMR.

Contact no: 04162282158

What will happen if you make your patient withdraw from this study after it starts?

Your patients' participation in this study is entirely a voluntary decision from you and you are also free to decide to withdraw permission for participation of the patient in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

We do not expect any injury to happen to patients but if any patient in the study does develop any problems due to the study, these will be treated at no cost.

Will you have to pay for the RMNS study?

RMNS study and post therapy EEG will be done free. Any other treatment that patients usually take will continue but the usual arrangements that you have with the hospital will decide how much you pay for this.

What happens after the study is over?

Patient may or may not benefit from the study. We expect an improvement in wakefulness, arousal and responsiveness of the patient after the therapy, as per the previous studies.

Will the personal details of the patient be kept confidential?

The results of this study will be published in a medical journal but the patient will not be identified by name in any publication or presentation of results. However, the patients' medical notes may be reviewed by people associated with the study, without your additional permission.

If the patient becomes conscious enough to communicate or indicate his/her dislikes later in the study they will explained about the therapy in the due manner and an additional consent from them will be obtained.

If you have any further questions, please ask Dr. Remya Mathew, Dr. Anand, Dr. Raji Thomas (telephone number: 0416 2282158) or email: pmr@cmcvellore.ac.in.

"If the patient (or you on his/her behalf) has any difficulty at any time in connection with this study which cannot be resolved by the doctors mentioned above, you may directly contact Dr. Nihal Thomas, Vice-Principal (Research) at 0416-2284294."

INFORMED CONSENT

Title of the study: **Right Median nerve electrical stimulation for patients with acquired brain injury who are in subnormal conscious state for increasing the wakefulness, arousal and responsiveness.**

Principal Investigator: Dr. Remya Mathew
Department: Physical Medicine and Rehabilitation (PMR), CMC, Vellore

I (name), (relation) of (patients' name), _____ have understood the details of the proposed study. The following aspects of the study have been explained to me in a comprehensible manner:

1. If I give consent to participate in this study, my(relation of patient) will be undergoing electrical stimulation of mild power ,to the right wrist nerve in hope of improving his/her arousal status.

2. It has been explained to me that the patient will be in one of the two groups. In one of they will receive stimulation, and in the other group the patient will receive sham stimulation, the meaning and purpose of which is explained to me. Which is the group in which my patient is recruited will be revealed neither to me nor to the investigating doctor.

3. Usage of stimulator is not likely to adversely affect patient's health in any foreseeable manner.

4. I can choose not to give consent to take the patient to be part of this study. I can also choose to withdraw my (relation) from the study at any time without being obliged to provide an explanation. In any case, my decision will not affect the treatment given to the patient in this hospital.

I am willing to give consent for including my (relation) to be part of this study voluntarily and without any coercion from the investigators of this project.

Signature of patient's Responsible relative

Signature of investigator

Signature of witness
Date:

PROFORMA FOR THE STUDY OF RIGHT MEDIAN NERVE ELECTRICAL STIMULATION FOR PATIENTS WITH ACQUIRED BRAIN INJUIRY WHO ARE IN IMPAIRED CONSCIOUSNESS.

Sl . No:

Group: control/experimental

Age in years:

Sex:

Duration of injury: in weeks

(Duration of injury at the first day of enrollment into study)

Mode of brain injury:

a) Traumatic:

b) Non traumatic:

If traumatic-

Diffuse axonal injury: Present/absent

Decompression surgery: done/not done

History of seizures:

Initial consciousness status:

a) Vegetative

b) Minimally conscious state

Abnormal posturing: (decerebration /decortications- present / absent)

Blood Parameters:

Serum. Sodium

Serum. Potassium

Administration of neuro stimulatory drugs: (Syndopa, Amantadine, Zolpidem, Modafinil)

OUTCOME PARAMETERS:

PARAMETER	PRE THERAPY	POST THERAPY
CRS-R SUBSCALES		
WHIM-max* WHIM-Total*		
RLAS		
GOSE		

WHIM-max→BEST LEVEL ATTAINED BY THE PATIENT ACCORDING TO WHIM SHEET*

WHIM-Total→ Total scoring observed within that maximum score in WHIM scale*

PARAMETERS FOR QUALITATIVE ANALYSIS:

1. EEG pattern

2. SSEP – Somato sensory evoked potential for right median nerve

3. VEP pattern- Visual Evoked potential

4. BERA pattern- Brain stem evoked auditory response

5. SSEP Tibial pattern- Somato sensory evoked potential for tibial nerve.

JFK COMA RECOVERY SCALE - REVISED ©2004

Record Form

This form should only be used in association with the "CRS-R ADMINISTRATION AND SCORING GUIDELINES" which provide instructions for standardized administration of the scale.

Patient:	Diagnosis:	Etiology:
Date of Onset:	Date of Admission:	

Date																
Week	ADM	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
AUDITORY FUNCTION SCALE																
4 - Consistent Movement to Command *																
3 - Reproducible Movement to Command *																
2 - Localization to Sound																
1 - Auditory Startle																
0 - None																
VISUAL FUNCTION SCALE																
5 - Object Recognition *																
4 - Object Localization: Reaching *																
3 - Visual Pursuit *																
2 - Fixation *																
1 - Visual Startle																
0 - None																
MOTOR FUNCTION SCALE																
6 - Functional Object Use †																
5 - Automatic Motor Response *																
4 - Object Manipulation *																
3 - Localization to Noxious Stimulation *																
2 - Flexion Withdrawal																
1 - Abnormal Posturing																
0 - None/Flaccid																
OROMOTOR/VERBAL FUNCTION SCALE																
3 - Intelligible Verbalization *																
2 - Vocalization/Oral Movement																
1 - Oral Reflexive Movement																
0 - None																
COMMUNICATION SCALE																
2 - Functional: Accurate †																
1 - Non-Functional: Intentional *																
0 - None																
AROUSAL SCALE																
3 - Attention																
2 - Eye Opening w/o Stimulation																
1 - Eye Opening with Stimulation																
0 - Unarousable																
TOTAL SCORE																

Denotes emergence from MCS†

Denotes MCS*

WHIM
The Wessex Head Injury Matrix
Scoring sheet

General instructions

Start at item one of the matrix (which starts on page 2).

Tick/check all behaviours observed and cross those not observed.

Once you have 10 consecutive crosses: stop.

In the Score summary (below) record, as the score, the number of the most advanced behaviour that has been observed (ticked/checked).

Patient details

Name

Date of birth

Date of injury

Age

Gender ☐ Male ☐ Female

Hospital

Unit/ward

Hospital number

Score summary

Assessment number	Score (i.e. number of the most advanced behaviour observed)	Date	Name of assessor	Stimulus used	Assessment conditions	Duration of observation	Total number of behaviours observed during the session
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							

24	Maintains eye-contact for 5 seconds or more	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Looks at person for 5 seconds or longer.
25	Silent mouthing	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Word like shapes being formed by mouth e.g. 'hello'. Does not include chewing movements.
26	Frowns, grimaces, etc. to show dislike	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Observed while having blood taken, chest physio (esp. if suction). Passive limb movements if has increased tone and contractures. While sitting up or being placed on tilt table.
27	Is able to ignore distraction	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	When patient is giving attention e.g. looking at someone talking patient can ignore distraction as appropriate e.g. when someone comes into the room.
28	Looks at object when requested	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Hold up brightly coloured object out of patient's immediate view and ask patient to look at it.
29	Choose an object when requested	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Choice of two objects both within visual range but far enough apart for patient to have to move eyes to look from one to the other. Ask patient to look at object on the right. Ask patient to look at object on the left. Change object and repeat.
30	Laughs	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Patient makes sounds/movements to express amusement, may appear appropriate or inappropriate.
31	Imitates gesture (blink x 2, thumb up, etc.)	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Verbal cue (instruction) and demonstration given to the patient. Patient is requested to imitate gesture and must do so clearly to request (confirm by repeating procedure if in doubt).
32	Indicates understanding by headshake, nod, gesture, etc.	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Establish that the patient can signal yes/no reliably by presenting a list of 10 questions. Patient must be correct 9/10.
33	Seeks eye contact	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Moves head or eyes in order to make eye contact and maintains this for at least three seconds.
34	Monosyllabic or single words in response to questions	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Single syllables or single words... 'yes', 'no' etc.
35	Looks at, and apparently explores, pictures, magazine, T.V. etc.	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Pictures e.g. family photographs – looks at one, puts down, looks at another; Magazine – turns pages; TV – watches for appropriate duration – scene of programme... duration of TV advert..., music video etc.
36	Switches gaze from one person to another, spontaneously	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Two people present in room positioned so that patient's eyes must move or head must be turned to switch gaze from one to the other. Spontaneously looks from one person to the other.
37	Speech is fluent but rambling. Lots of words but meaning hard to understand	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Patient jumps from subject to subject or gives excessive details, doesn't answer questions or keep to the subject of conversation.
38	Looks for object that has been shown and then removed from line of vision	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Large bright object which is easy to see and is meaningful to the patient is shown to the patient for 15 seconds. Object is then removed and placed where it cannot be seen eg underneath bedclothes within patients reach. Patient may use any medium to indicate where object is (e.g. gesture, speech, eye, pointing etc).
39	Can attend to task, TV etc., but concentration is vulnerable; any external stimulus distracts	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Attend to task for 1 minute while no distraction. Any distraction immediately diverts attention and attention does not return to task.
40	Monosyllabic or single words to express mood or need	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	'Tired', 'hungry', 'thirsty', 'pain' etc. ... words are used singly and sentences are never used.
41	Is momentarily distracted by external stimulus but can return to task	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Momentarily = no longer than 10 seconds.
42	Can find a specific playing card from a selection of four	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Four playing cards presented, 2 black, 2 red, and 2 number, 2 picture in any combination. Patient is asked to select one card. Ten trials. (9/10 correct)
43	Smiles	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Spontaneous smile for any reason.
44	Uses writing, typing or other communication aid, but is hard to understand	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Makes an attempt to write name or word. Write rather than sign name. Some letters recognisable
45	Can say what part of day it is	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Give patient 3 options – morning, afternoon, evening or use mealtimes rather than am or pm if preferred... e.g. after breakfast and before lunch etc.
46	Brief phrases	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Phrases or incomplete sentences
47	Points with eyes	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Choice of two pictures or real objects or 'yes/no' cards. Must eye point correctly on 9/10 trials.
48	Initiates conversation	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Attracts attention of another person by sound or physical gesture. (Note: speech not necessary)

49	Vocalises to attract attention	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Those in room do not give attention... e.g. talk to each other... patient makes any sound to attract attention.
50	Speech is established, but the content is indicative of problems with word-finding or difficulty in comprehension.	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Patient is able to follow double command, but not more i.e. 'lift your arm and squeeze my hand'. Has difficulty expressing himself/herself or naming objects.
51	Conventional speech usage but with very few words	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Shortening of sentences. States facts only, giving little or no description.
52	Uses one or two gestures	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Thumbs up/down. Nod/shake head. May be spontaneous or in response to prompt
53	1 or 2 orientation items correct (day of week, month, year, age, place)	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Ask patient: 'What day is it?'; 'What month is it?'; 'What age s/he is?'; 'Where s/he is now?' (hospital & city). If patient does not know answers, give correct information.
54	Knows the price of 3 common objects (bread, pint of beer, milk, etc.) to within a few pence/dimes	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Objects: such as audio cassette, chocolate bar, can of Coca-Cola®. Reasonably accurate price must be given for all three on the same occasion.
55	Recognises coins (eye-point or touch named coin)	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	3 coins are presented... 2p, 50p and £1 (Dime, Nickel, Quarter). Coins are presented in a row in the following order: 50p/Nickel ... 2p/Dime ... £1/Quarter. Patient asked to point to 2p/Dime ... £1/Quarter ... 50p/Nickel.
56	Knows the name of one member of staff	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Spontaneously calls staff member by name or remembers name when asked. (Check patient is not reading name from name badge).
57	Names or indicates left and right on self	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Follows instructions e.g. raise right hand; raise left hand; turns head to right; turns head to left or similar.
58	Uses writing, typing or other communication aid fluently	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Message can be easily understood by anybody.
59	3–5 orientation items correct	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Procedure and orientation items as above.
60	Remembers something from the day before (e.g. show a coin, key, watch, etc. from your pocket and say you will ask them to remember it tomorrow).	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Show patient item. Put it in pocket and tell patient you will ask the following day what is in their pocket, etc. Next day, ask patient if s/he can remember. If patient cannot remember, give choice of three e.g. 'was it a watch, a key or a 50p coin?'. Record if patient recognises correct response.
61	Remembers something from earlier in the day (e.g. 'Have you been to physio yet?')	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	Check what has happened that day. Choose an event which does not happen invariably in the morning or afternoon. Opening question given e.g. 'What have you done this morning?'. Follow this by prompt if no answer e.g. 'What did you do at physio this morning?'.
62	Out of Post Traumatic Amnesia	☐☐☐☐☐ ☐☐☐☐☐ ☐☐☐☐☐	

RANCHO LOS AMIGOS SCALE

AKA Level of Cognitive Functioning Scale (LCFS)

____ (1) **Level I** - No Response.
Patient does not respond to external stimuli and appears asleep.

____ (2) **Level II** - Generalized Response.
Patient reacts to external stimuli in nonspecific, inconsistent, and nonpurposeful manner with stereotypic and limited responses.

____ (3) **Level III** - Localized Response.
Patient responds specifically and inconsistently with delays to stimuli, but may follow simple commands for motor action.

____ (4) **Level IV** - Confused, Agitated Response.
Patient exhibits bizarre, nonpurposeful, incoherent or inappropriate behaviors, has no shortterm
recall, attention is short and nonselective.

____ (5) **Level V** - Confused, Inappropriate, Nonagitated Response.
Patient gives random, fragmented, and nonpurposeful responses to complex or unstructured stimuli - Simple commands are followed consistently, memory and selective attention are impaired, and new information is not retained.

____ (6) **Level VI** - Confused, Appropriate Response.
Patient gives context appropriate, goal-directed responses, dependent upon external input for direction. There is carry-over for relearned, but not for new tasks, and recent memory problems persist.

____ (7) **Level VII** - Automatic, Appropriate Response.
Patient behaves appropriately in familiar settings, performs daily routines automatically, and shows carry-over for new learning at lower than normal rates. Patient initiates social interactions, but judgment remains impaired.

____ (8) **Level VIII** - Purposeful, Appropriate Response.
Patient oriented and responds to the environment but abstract reasoning abilities are decreased relative to premorbid levels

Glasgow Coma Outcome scale Extended

1 Dead

2 Vegetative state (VS)
No cerebral cortical function that can be judged by behaviour (not able to follow simple commands or communicate)

3 Lower severe disability (lower SD)
Needs full assistance in ADL throughout the day

4 Upper severe disability (upper SD)
Needs some supervision/assistance in ADL, but can be alone for >8 h/d

5 Lower moderate disability (lower MD)
Independent in ADL, and can shop and travel independently on public transportation, but has not returned to previous position or lifestyle

6 Upper moderate disability (upper MD)
Able to resume previous position or lifestyle with alternative/modified duties or part-time due to injury

7 Lower good recovery (lower GR)
Able to resume previous position or lifestyle (may be modified), but reporting some problems

8 Upper good recovery (upper GR)
Complete return to previous lifestyle with no reported Problems